

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022555Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Pharmacoepidemiology and Statistical Science  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** 22555  
**Drug Name:** AI-700 Hexvix  
**Indication(s):** Adjunct to white light cystoscopy in the detection of non-muscular invasive papillary cancer of the bladder  
**Applicant:** Photocure ASA  
**Date(s):** Stamp: 6 – 30 - 09 PDUFA: 12 – 30 - 09  
**Review Priority:** Priority

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**Keywords:** Clinical Studies , Imaging , Sensitivity , Specificity , Accuracy , Non-inferiority

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# **1. EXECUTIVE SUMMARY**

## **1.1 Conclusions and Recommendations**

Photocure submitted NDA 22555 on June 30 2009 , and the Agency directed that it be reviewed under priority status, with the PDUFA date set as December 30 2009. The submission included only one primary Phase III Study of the Sponsor's Test drug Hexvix - Study#305/04. This trial investigated the efficacy of a combination White Light/Hexvix Blue Light cystoscopy for detection of additional papillary bladder lesions, and for reduction of lesion "recurrence" (also called as "follow-up detection" in the clinical review to more appropriately convey the clinical interpretation of these data) when compared to standard White Light cystoscopy taken alone. The efficacy objective were, therefore, to show that a combination baseline White Light/Blue Light evaluation detected lesions missed by standard White Light cystoscopy, and that subsequent cystoscopies were less likely to present "new" (not detected previously) lesions (not to be interpreted as lesions newly formed not existing previously) than would a baseline standard White Light cystoscopy. The Study randomized subjects to a Hexvix Arm and a White Light Arm. Subjects in both arms underwent a baseline White Light cystoscopy for detection of bladder lesions ; subjects in the Hexvix Arm also underwent a Hexvix Blue Light examination during the same cystoscopy for detection of additional lesions. Subsequently, subjects in both arms were followed for nine months for detection of early lesion recurrence. The Hexvix Arm therefore played two roles: evaluation of additional lesion detections under combination White Light/Hexvix Blue Light cystoscopy, and evaluation of levels of lesion recurrence when compared to the recurrences in the Comparator White Light Arm. The protocol stipulated that the demonstration of Hexvix efficacy required not only statistically significantly improved detection, but also statistically significant reduced recurrence, both at the 1% level of significance. The Sponsor met the improved Detection endpoint., but not the reduced recurrence endpoint.

## **1.2 Brief Overview of Clinical Studies**

The single Primary Phase III trial, Study305/04, enrolled 814 subjects from 28 centers in US/Canada and Europe. The study was initiated in January 2005 and completed in September 2007. Subjects qualified for enrollment if they had confirmed initial or recurrent bladder cancer of type Ta/T1 and no lesions confirmed as Type T2 or higher at time of enrollment. Subjects were randomized to two arms. There were 430 subjects enrolled into the Hexvix Arm, which was dedicated, first, to evaluation of the lesion detection endpoint, and next, to evaluation of the lesion recurrence endpoint. A total of 286 of the 430 subjects in the Hexvix Arm had Ta/T1 positive histology results from Central Panel histology and these constituted the ITT population for evaluation of the detection endpoint. A total of 271 of the 430 subjects had Ta/T1 positive histology results from local histology, with no lesions of type T2 or higher, and these subjects constituted the ITT Hexvix Test population for evaluation of the recurrence endpoint. There were 384 subjects enrolled into the White Light Arm. There were 280 among the 384 subjects in the White Light group with confirmed Ta/T1 results from local histology, and these subjects constituted the ITT White Light Comparator population for evaluation of the recurrence endpoint.

There were two co-primary criteria for success for Hexvix evaluations: Improved detection of Ta/T1 lesions for subjects evaluated under combination White Light/Hexvix Blue Light cystoscopy, and reduced lesion recurrence for subjects evaluated under the combination cystoscopy when compared to subjects evaluated under White Light cystoscopy only. The criteria were set high: hypotheses of at most 10% increased detections and of no differences in rates of recurrence were simultaneously to be rejected at a level  $\alpha = .01$  (rather than the typical .05). The Sponsor met the detection rate criterion (  $p\text{-value} < .001 < .01$  ), but failed with the recurrence criterion (  $p\text{-value} = .027 > .01$  ).

### 1.3 Statistical Issues and Findings

#### Detection Endpoint Finding

The proposed advantage of the combination White Light/Hexvix Blue cystoscopy over White Light only cystoscopy is that the combination is likely to detect positive lesions missed by White light. The Sponsor pre-specified that the combination evaluation should detect additional Ta/T1 lesions in more than 10% of the subjects. This pre-specified goal was met. However, when the analyses were stratified by continent, the goal was met in the US/Canada, where center enrollments were small ( median enrollment = 5 patients ), but not in Europe, where center enrollments were large ( median enrollment = 17 patients).

The table below presents the point estimates, along with 2-sided 99% CI's , both overall and by continent. The Reviewer suggests that investigator expertise with White Light could account for the absence of improved Hexvix efficacy in the large centers.

**Table(1):  
Primary Subject Level Results for the Detection Endpoint  
(Categories: Overall ; by Continent )**

	# Subjects	New Detections ( Blue Light)	New Detection Rate	p-values
<b>Overall</b>	<b>286</b>	<b>47</b>	<b>16%</b>	<b>p &lt; .01 Criterion met</b>
<b>US/Canada ( 19 Centers ) ( Median Subjects/Center = 5)</b>	<b>121</b>	<b>29</b>	<b>24%</b>	<b>p &lt; .01 Criterion met</b>
<b>Europe ( 9 Centers ) ( Median Subjects/Center = 17 )</b>	<b>165</b>	<b>18</b>	<b>11%</b>	<b>p &gt; .01 Criterion not met</b>

## Recurrence Endpoint Finding

For several reasons – loss to follow-up , absence of cystoscopy data – approximately 20% of the subjects in both the Hexvix Arm and the White Light Arm had to have their findings imputed, and the Sponsor chose a “Worst Outcome” imputation, namely, that all such subjects would be imputed as recurrent for positive lesions. These 20% of subjects with imputed recurrences constituted approximately 40% of all recurrences in each arm, that is, on the average, for every 5 recorded recurrences, 3 were actually validated and 2 were imputed. This imputation scheme, when compared to an alternative scheme, impacts the efficacy statistics to the disadvantage of Hexvix . The Reviewer’s choice for an alternative scheme was an “Extrapolation” imputation, in which subjects with missing data were provided with recurrence probabilities consistent with validated recurrence probabilities. The point estimates and 2-sided 99% CI’s for differences in rates achieved under these two schemes are listed below:

### *Sponsor’s Results under Worst Case Imputation*

*White Light Arm Recurrence Rate = 56% ; Hexvix Arm Recurrence Rate = 47 %  
Difference in rates = 9%  
2-sided 99% CI for difference is ( -2% , 20%) Lower limit of CI does not exceed zero.*

### *Reviewer’s results under Extrapolation Imputation:*

*White Light Arm Recurrence Rate = 44% ; Hexvix Arm Recurrence Rate = 33%  
Difference in rates = 11%  
2-sided 99% CI for difference is ( 0% , 22%) Lower limit of CI is slightly above zero.*

Thus, in a context where White Light recurrence rates are concluded to be in excess of Hexvix recurrence rates if the lower limit of the 2-sided 99% CI exceeds zero, it is seen that the Worst Case imputation works to the disadvantage of Hexvix.

## Lesion Level Findings

The Sponsor’s primary objectives were *subject level* objectives:

- (a): Efficacy in Detection was interpreted to mean that Hexvix found at least one Ta/T1 lesion missed by White Light in more than 10% of the subjects.
- (b): Efficacy in Recurrence ( detection of “new” positive lesions during early follow-up ) was interpreted to mean that a smaller percentage of Hexvix Arm subjects had recurrences than did White Light Arm subjects.

Both objectives could be met even if Hexvix was no better than White Light in positive lesion detections. In fact, there was effective parity between Hexvix and White Light in lesion level detections, as displayed in the table below. It should be noted that Hexvix and White Light presented equivalent statistics on histologically confirmed Ta/T1 lesions, while Hexvix was more likely to produce false positives.

**Table(2): Overall Lesion Level True Positive / False Positive Detection Profile**

	<b># Lesions</b>	<b>White</b>	<b>Blue</b>	<b>White&amp;Blue</b>	<b>White not Blue</b>	<b>Blue not White</b>
<b>True Positive Profile</b>	<b>675 (Ta/T1 Positives)</b>	<b>90%</b>	<b>91%</b>	<b>81%</b>	<b>9%</b>	<b>10%</b>
<b>False Positive Profile</b>	<b>142 (Normals)</b>	<b>68%</b>	<b>85%</b>	<b>53%</b>	<b>15%</b>	<b>32%</b>

Further details on these findings will be presented in the Statistical Evaluation section below.

## 2. INTRODUCTION

### 2.1 Overview

Photocure provided only one primary Phase III study in NDA22555 in support of an indication for Hexvix Blue Light cystoscopy for detection of bladder lesions. This single Primary Phase III trial, Study305/04, enrolled 814 subjects from 28 centers in US/Canada and Europe. The study was initiated in January 2005 and completed in September 2007. Subjects qualified for enrollment if they had confirmed initial or recurrent bladder cancer of type Ta/T1 and no lesions confirmed as Type T2 or higher at time of enrollment. Subjects were evaluated for lesion detection and for lesion recurrence, with the lesion detection evaluation performed first, during a baseline cystoscopy, and the lesion recurrence evaluation performed over a nine month period subsequent to the baseline evaluation.

Subjects were randomized to two arms- the Hexvix Arm and the White Light Arm. There were 430 subjects enrolled into the Hexvix Arm, which was dedicated to both efficacy objectives: first, to the evaluation of the lesion detection endpoint, and next, to the evaluation of the lesion recurrence endpoint. Hexvix Arm Subjects underwent a sequential White Light/Hexvix Blue Light examination under a baseline cystoscopy, and all detected lesions, under either White Light or the subsequent Blue Light, were evaluated as positive or normal through both a local histology and a Central Panel histology. A total of 286 of the 430 subjects in the Hexvix Arm had Ta/T1 positive results from the Central Panel histology, and these subjects constituted the ITT population for evaluation of the detection endpoint. A total of 271 of the 430 subjects had Ta/T1 positive results from local histology, and no confirmed lesions of type T2 or higher, and these subjects constituted the ITT Hexvix Test Arm population for evaluation of the recurrence endpoint. There were 384 subjects enrolled into the White Light Arm, and these subjects also underwent a baseline cystoscopy, but with White Light only. There were 280 among the 384 subjects in the White Light group with confirmed Ta/T1 results from local histology, and these subjects constituted the ITT White Light Comparator population for evaluation of the recurrence endpoint.

There were two co-primary criteria for success for Hexvix evaluations: Increased detection of Ta/T1 lesions for subjects evaluated under the baseline combination White Light/Hexvix Blue Light cystoscopy, and reduced lesion recurrence for subjects evaluated under the baseline combination cystoscopy when compared to subjects evaluated under the baseline White Light cystoscopy only. Subjects were scheduled for evaluation under White Light cystoscopy for lesion recurrence at 3, 6, and 9 months post Baseline.

Detection: The subject level increase in Ta/T1 detections for Blue Light over White Light had to exceed 10% , with a significance level set at .01 .

Recurrence: The subject level recurrence rate for the Hexvix Arm had to be less than the recurrence rate for the White Light Arm, again with a significance level set at .01.

The Sponsor met the detection rate criterion, with 16% of the subjects presenting with additional Ta/T1 lesions under Hexvix Blue Light (  $p\text{-value} < .001 < .01$  ). The Sponsor failed the recurrence criterion: the 56% White Light recurrences were not sufficient to achieve significance over the 47% Blue Light recurrences with alpha set at .01 ( the actual p-value achieved was  $p=.027 > .01$  ). This performance was influenced by the imputation scheme for missing data. An exploratory analysis using an alternative imputation scheme will be presented below in order to highlight the sensitivity of the results to the imputations.

## **2.2 Data Sources**

The data in this submission was provided by Photocure electronically. All the data files were accessible and in appropriate format. The definition files submitted were adequate to facilitate the review.

### 3. STATISTICAL EVALUATION

#### 3.1 Evaluation of Efficacy

**The Sponsor submitted only one primary Phase III Study: PC305/04**

**Study Title:** A randomized, comparative, controlled Phase III multicenter study of Hexvix fluorescence cystoscopy and white light cystoscopy in the detection of papillary bladder cancer and the early recurrence rate in patients with bladder cancer.

*There were two Co- Primary Study Objectives*

**(1): Detection Objective:** To compare Hexvix cystoscopy with white light cystoscopy in the detection of histologically confirmed papillary bladder cancer in patients with papillary bladder cancer.

**Specifically:** *To determine, during a single cystoscopy of a subject, where a Hexvix Blue Light evaluation follows a White Light evaluation: If Hexvix Blue Light detects a lesion missed by White Light that is subsequently confirmed as a Ta/T1 lesion by a Central Panel histology.*

**(2): Recurrence Objective:** To compare early recurrence rate after Hexvix and white light transurethral resection (TURB) with white light TURB in patients with non-muscle invasive bladder cancer.

**Specifically:** *To determine if subjects who undergo White Light followed by Hexvix Blue Light cystoscopy are less likely to have lesion recurrences during a nine month follow-up than are subjects who undergo White Light cystoscopy only.*

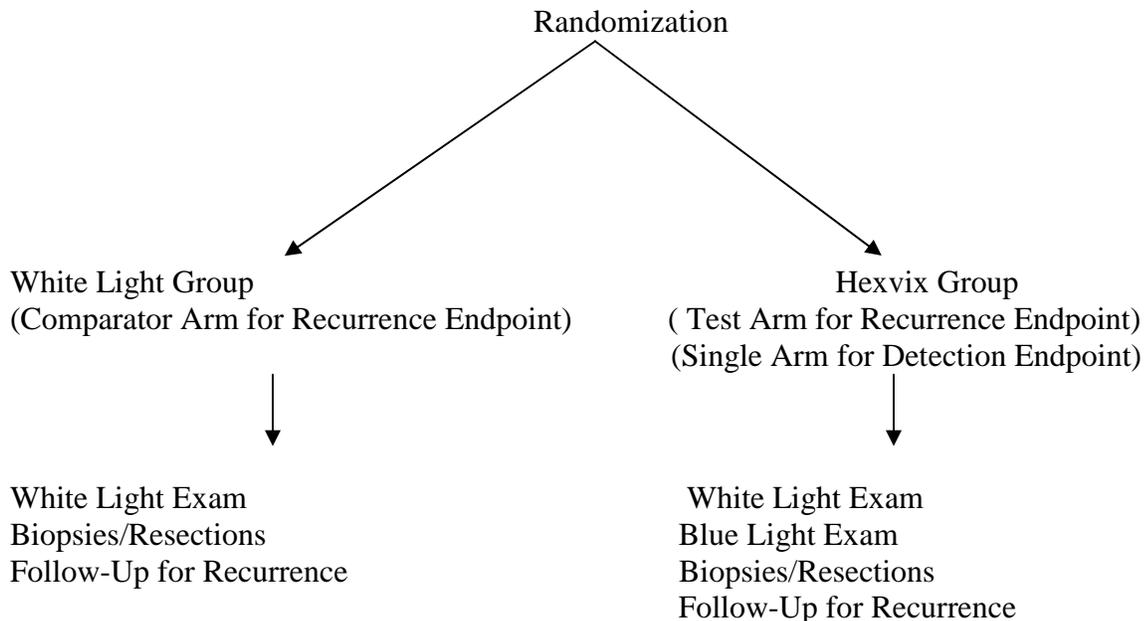
## Overview of Protocol

**Inclusion Criteria:** A Subject had to fulfill at least one of the following requirements:

- (1): Subject had an initial papillary bladder tumor confirmed on outpatient cystoscopy.
- (2): Subject had *more than one* papillary lesion recurrence confirmed on an outpatient cystoscopy.
- (3): Subject had *one or more* papillary lesion recurrences confirmed on an outpatient cystoscopy within 12 months of a previous cystoscopy.

### Randomization Procedure:

Evaluation of the two primary endpoints required that subjects be randomized to one of two arms: Hexvix Arm or White Light Arm. The subjects in the Hexvix Arm formed the exclusive population for evaluation of the Detection endpoint; they also were the Test subjects for evaluation of the Recurrence endpoint. The subjects in the White Light Arm formed the Comparator population for the Recurrence endpoint only. The White Light Arm subjects underwent White Light cystoscopy for detection of lesions. All lesions were resected, and the subjects were then followed for nine months with repeat cystoscopies at three month intervals for detection of lesion recurrence. The Hexvix Arm subjects underwent White Light cystoscopy followed by Hexvix Blue Light cystoscopy for detection of lesions. Resections were performed only after both the White Light and Blue Light examinations. Subjects in this arm were then followed for nine months with repeat cystoscopies at three month intervals for detection of lesion recurrence. Randomization was conducted so that the mix of subjects with initial papillary lesions or recurrent lesions was balanced between the arms. A schematic is shown below.



### **Further details relevant to the Detection Endpoint:**

(1): Investigators/subjects in the Blue Light Arm knew it was the Blue Light Arm. However, not all patients within the arm underwent Blue Light evaluations. A blinded randomization to discontinue to Blue Light evaluations occurred only after the White Light evaluation. This procedure was put in place to safeguard against potential under-calling of lesions by White Light.. (13 subjects did not continue to Blue Light. )

(2):Resections in the Hexvix Blue Light arm were to be performed only after both White Light and Blue Light detections were registered.

(3): For the detection endpoint evaluations, Truth Standard confirmation of the disease status of all detected lesions was to be provided by a central pathology lab. However, local histology ( relevant to the recurrence endpoint ) was also to be performed.

(4): The ITT population for the Detection Endpoint was defined as the set of subjects in the Hexvix Arm who:

(a): Received Hexvix installation and were evaluated under both White and Blue Light.

(b): Had a central panel histology confirmation ( positive or negative) for at least one lesion, detected under White Light or Blue Light.

### **Further details relevant to the Recurrence Endpoint:**

(1): Subjects from both arms who had at least one detection confirmed as Ta/T1 by local histology were followed for recurrence. These subjects formed the ITT population.

(2): Lesions of any positive type constituted recurrences. That is, although subjects needed to be Ta/T1 positive for the initial cystoscopy in order to qualify for follow-up, recurrences in these subjects were any locally confirmed positive lesions - Types Ta/T1, CIS , T2 or higher.

(3): Evaluations for recurrence were to be performed at 3 , 6 , and 9 months post the initial cystoscopy. If local histology confirmed a recurrence at one of these time points, the subject was classified as recurrent and subsequent evaluations were not necessary.

(4): Subjects could be lost to follow-up, where “ Loss to Follow-Up” means that there was a scheduled time point ( 3, 6, 9 months) for which, and after which, a subject not previously confirmed for recurrence did not present for cystoscopy. Such subjects were imputed as “Worst Outcome” cases, namely, as recurrent for disease.

## Primary Endpoint Hypotheses

### Hypotheses for the Detection Endpoint:

Let  $\pi_H$  = Proportion of subjects who have at least one papillary lesion confirmed by central pathology ( Standard of Truth Panel Read ) that was detected under Blue light and not detected under White Light. Then:

Null Hypothesis:  $\pi_H = .10$  ; Alternative Hypothesis:  $\pi_H \neq .10$

The alpha level set for rejection of the Null is .01 . The more customary alpha level of .05 was ruled out because the Sponsor provided only one Phase III Study. The stipulated statistic was an Exact Test for a single proportion.

**Comment:** *The intention here is to show that  $\pi_H > .10$  . The Sponsor's conclusion would be that  $\pi_H > .10$  follows if the Null is rejected and the point estimate for  $\pi_H$  exceeds .10*

### Hypotheses for the Recurrence Endpoint:

Let  $\pi_H$  = Proportion of subjects in the Blue Light Arm with tumor recurrence confirmed by local pathology.

Let  $\pi_S$  = Proportion of subjects in the White Light Arm with tumor recurrence confirmed by local pathology.

Then:

Null Hypothesis:  $\pi_H = \pi_S$  ; Alternative Hypothesis:  $\pi_H \neq \pi_S$

Once more the alpha level was set at .01. The stipulated statistic was the Cochran-Mantel-Haenszel Chi-Square Test with stratification by center.

**Comment:** *The intention here is to show that  $\pi_H > \pi_S$  . The Sponsor's conclusion would be that  $\pi_H > \pi_S$  follows if the Null is rejected and the point estimate for  $\pi_H - \pi_S$  exceeds zero.*

### Comments on Overall Success per these hypotheses:

*The Sponsor's intention was to test for Detection first, and, if successful, to subsequently test for Recurrence. Success on Detection alone, however, would not be viewed by the Agency as sufficient for a Detection indication. Success for both endpoints would be required for a detection indication; positive results for recurrence serve primarily as supportive of positive results for detection.*

## Relevant Secondary Endpoints

A demonstration that Hexvix Blue Light provides a subject level advantage for Ta/T1 detections over White Light would imply only that, with statistical significance, a Blue Light evaluation subsequent to a White Light evaluation, would detect at least one Ta/T1 lesion missed by White Light. This does not imply that Blue Light detects every Ta/T1 lesion detected by White Light, and then, something more. Logically, it is possible that White Light is more successful on Ta/T1 detections, lesion by lesion. The proposed advantage of the Hexvix Blue Light evaluation is that it finds “other”, not that it finds more. In order to better understand the distinction between a subject level performance and a lesion level performance for Blue Light versus White Light, several lesion level analyses were provided in the protocol. The reviewer sometimes imposed a few refinements on these analyses. These modified analyses, intended as purely descriptive, will be presented as part of the Trial Results material below.

## Trial Results on Detection: Subject Level

Since the ITT Efficacy Study includes a parallel group comparison for the Recurrence Endpoint, it is important that the groups be balanced with respect to demographics and bladder disease history:

**Table(3): Demographics**

Group	ITT Population		Safety Population	
	Hexvix	White Light	Hexvix	White Light
<b>Number of Subjects</b>	<b>365</b>	<b>361</b>	<b>421</b>	<b>381</b>
<b>Age</b>	<b>69 +/-11 yrs ( 39 yrs, 94 yrs)</b>	<b>70 +/- 11 yrs (24 yrs, 94 yrs)</b>	<b>69 +/-11 yrs ( 39 yrs, 94 yrs)</b>	<b>70 +/- 11 yrs (24 yrs, 94 yrs)</b>
<b>Gender</b>				
<b>Male</b>	<b>278 (76%)</b>	<b>284 (79%)</b>	<b>322 (77% )</b>	<b>301 (79%)</b>
<b>Female</b>	<b>87 ( 24%)</b>	<b>77 (21%)</b>	<b>99 (23%)</b>	<b>80 ( 21%)</b>
<b>Ethnic Group</b>				
<b>White</b>	<b>337 (92%)</b>	<b>345 ( 96%)</b>	<b>386 ( 92%)</b>	<b>364 ( 96%)</b>
<b>Black</b>	<b>8 ( 2%)</b>	<b>5 ( 1%)</b>	<b>11 (3%)</b>	<b>5 ( 1%)</b>
<b>Other</b>	<b>20 (6%)</b>	<b>11 (3%)</b>	<b>24 (5%)</b>	<b>12 ( 3%)</b>
<b>Bladder Cancer History</b>				
<b>Initial</b>	<b>149 (41%)</b>	<b>152 (42%)</b>		
<b>Recurrent</b>	<b>216 (59%)</b>	<b>209 (58%)</b>		

**Table(4): Patient Disposition**

	<b>HEXVIX ARM</b>	<b>WHITE LIGHT ARM</b>
<b>Enrolled and Randomized</b>	<b>430</b>	<b>384</b>
<b>ITT Efficacy Population for Detection</b> <b>35 Subjects in Hexvix Training Set</b> <b>Hexvix Arm does not include:</b>  <b>13 others with Protocol ITT Violations</b> <b>13 Subjects discontinued ( No Blue Light)</b> <b>4 excluded from Safety Set</b>	<b>365</b>	
<b>ITT Detection Population with confirmed Ta/T1</b>	<b>286</b>	
<b>ITT Efficacy Population for Recurrence</b> <b>Only Subjects with confirmed Ta/T1 at Baseline</b>	<b>271</b>	<b>280</b>

**Results for the Primary Detection Endpoint**

The Sponsor achieved the pre-specified significance level for the Detection Endpoint:

There were 286 subjects with Ta/T1 lesions confirmed by the Central Panel.

There were 47 subjects among these 286 with a Ta/T1 lesion detected by Hexvix Blue Light and not by White Light. Thus, the observed proportion of such subjects was  $\pi = .16$ .

Under the Null Hypothesis, an observed  $\pi \geq .16$  or greater occurs with p-value  $< .001$ . This p-value is less than the pre-specified alpha of .01, so the Null is rejected, and the conclusion is that the True  $\pi > .10$ .

**Note(1):** An alternative approach consists in calculating a 2- sided 99% CI around the observed proportion to see if its lower limit exceeds .10. The CI is ( .11, .21 ) .Since the lower limit = .11  $> .10$ , this approach also confirms the Sponsor’s intended conclusion.

**Note(2):** As previously reported under Statistical Issues and Findings, the overall success with the Detection Endpoint is not replicated when subjects are stratified to continent. For completeness this finding is re-displayed below:

**Table(5):  
Primary Subject Level Results for the Detection Endpoint  
(Categories: Overall ; by Continent )**

	# Subjects	New Detections ( Blue Light)	New Detection Rate	p-values
<b>Overall ( 28 Centers)</b>	<b>286</b>	<b>47</b>	<b>16%</b>	<b>p &lt; .01 Criterion met</b>
<b>US/Canada ( 19 Centers ) ( Median Subjects/Center = 5)</b>	<b>121</b>	<b>29</b>	<b>24%</b>	<b>p &lt; .01 Criterion met</b>
<b>Europe ( 9 Centers ) ( Median Subjects/Center = 17)</b>	<b>165</b>	<b>18</b>	<b>11%</b>	<b>p &gt; .01 Criterion not met</b>

\* = Failure to meet the Detection Criterion :  $\pi_H > .10$

**Conclusions:**

(1): *The Sponsor met the Success Criterion over the entire population, but failed it under stratification to Continent .*

(2): *The European centers had larger enrollments ( Median = 17 subjects ) than the US/Canada centers ( Median = 5 subjects.) This correlation of continent with center size implies that the gain for Blue Light occurred primarily in small centers.*

**A complementary look at Subject Level Performance**

The positive overall Ta/T1 Detection results are compared below to a False Detection Profile at the Subject Level. The principal result on Ta/T1 Subject level Detections is included for completeness

**(1): Percentage of Subjects where Blue Light detects a Ta/T1 missed by White Light = 16%  
Percentage of Subjects where Blue Light detects a Normal missed by White Light = 13%**

**(2):For subjects with exactly one Normal Lesion, Subject Level False Detection Rates are:**

***White Light detects, Blue Light doesn't in 15% of the Subjects  
Blue Light detects, White light doesn't in 38% of the Subjects***

Thus, the Subject Level success in Ta/T1 detections is accompanied by complementary Subject Level “overcalling”.

**Trial Results on Detection: Lesion Level**

The subject level detection advantage of the combination White Light/Hexvix Blue Light cystoscopy is not sustained when detection results are focused on a lesion level. The comparisons of lesion level detection rates of Blue Light cystoscopy to White Light cystoscopy for histologically classified bladder lesions are presented below.

First, some conditions and definitions:

The Standard of Truth for tumor diagnosis was a protocol-specified Central Panel Read. It is important to keep in mind that the Standard of Truth is only applied to lesions detected by White Light and/or Blue Light. Thus, a lesion detected by White Light, say, which is subsequently confirmed to be Normal, is a False Positive for White Light.

**(1): Lesion Level True Positive ( TP) Detection Rates:**

There are two modalities: M = White Light or Blue Light  
 There are three Types of Positives Ta/T1 , CIS, or T2 and higher

$$\text{TP: Lesions Type T by Modality M} = \frac{\text{\#Lesion detections by M validated as Type T}}{\text{\# All detected lesions validated as Type T}}$$

**(2): Lesion Level False Positive (FP) Detection Rates:**

There are two modalities: M = White Light or Blue Light  
 There is only one lesion type: Normal

$$\text{FP: Normal Lesions detected by Modality M} = \frac{\text{\# Normal Lesions detected by M}}{\text{\# Normal lesions}}$$

**Table(6): Overall Lesion Level True Positive / False Positive Detection Profile**

	# Lesions	White	Blue	White&Blue	White not Blue	Blue not White
<b>True Positive Profile</b>	<b>675</b> (Ta/T1 Positives)	<b>90%</b>	<b>91%</b>	<b>81%</b>	<b>9%</b>	<b>10%</b>
<b>False Positive Profile</b>	<b>142</b> (Normals)	<b>68%</b>	<b>85%</b>	<b>53%</b>	<b>15%</b>	<b>32%</b>

**Comments:**

(1): The Profile for Blue Light versus White Light on Positives ( all types) reveals essentially equivalent performances.

(2): The Profile for Blue Light versus White Light on Normals reveals considerably less agreement, and a tendency for Blue Light to call more False Positives than White Light..

**A second look at Lesion Level performance:**

The analysis above works “backwards “ from histology to detections. The table below provides an alternative “ forwards” profile from detections to histology, and is included for completeness.

**Table(7): Profile of False Detection Rates ( (1 – Positive Predictive Value)x100% )**

	<b>Total Detections</b>	<b>Confirmed Normals</b>	<b>False Detection Rate</b>
<b>Blue Light</b>	<b>988</b>	<b>120</b>	<b>12%</b>
<b>White Light</b>	<b>917</b>	<b>97</b>	<b>11%</b>
<b>Blue &amp; White</b>	<b>791</b>	<b>75</b>	<b>9%</b>
<b>Blue not White</b>	<b>197</b> (20% of Blue Detections)	<b>45</b>	<b>23%</b>
<b>White not Blue</b>	<b>126</b> ( 14% of White Detections)	<b>22</b>	<b>17%</b>

**Detection Results by Lesion Type**

The analyses above demonstrate that the subject level detection advantage of a combination White Light/Blue Light cystoscopy for Ta/T1 lesions is not replicated on a lesion level. However, further differentiation of lesion level analyses by lesion type do reveal a trend away from parity in performance.

**Table(8): Lesion Level Detections by Lesion Type**

<b>Type of Lesion (Confirmed)</b>	<b>White&amp;Blue</b>	<b>White not Blue</b>	<b>Blue not White</b>
<b>Ta/T1</b> ( N = 675)	<b>548</b> ( 81%)	<b>62</b> (9%)	<b>65</b> (10%)
<b>CIS</b> ( N = 66 )	<b>33</b> (50%)	<b>6</b> (9%)	<b>27</b> (41%)
<b>T2/T4</b> ( N = 47)	<b>38</b> (81%)	<b>8</b> (17%)	<b>1</b> (2%)
<b>Normal</b> ( N = 142)	<b>75</b> (53%)	<b>21</b> (15%)	<b>46</b> (32%)

**Comments:** Although the sample sizes are insufficient for statistical inferences, there appear two trends in the data:

(a): White Light detects T2/T4 lesions with higher percentages than Blue Light

(b): Blue Light detects CIS lesions with higher percentages than White Light

*All the lesion level results above, when combined, suggest that White Light is as good or better than Blue Light in detection of lesions of type Ta/T1 and T2/T4, while Blue Light is more successful in detecting lesions of type CIS.*

## **Trial Results: Recurrence Endpoint**

**Restatement of Recurrence Objective:** *To determine if subjects who underwent the combination White Light /Hexvix Blue Light cystoscopy had lower rates of early recurrence than did subjects who underwent White Light cystoscopy only..*

**Note(1):** Early Recurrence is defined as tumors of any type – CIS, Ta, T1 or T2-T4 – that are detected by White Light and confirmed by local pathology during cystoscopies scheduled at 3, 6, and 9 months after the initial (Baseline) cystoscopy. A subject qualified for follow-up for recurrence if his/her baseline cystoscopy provided a lesion detection confirmed as Ta/T1 by local histology. The recurrence endpoint evaluation in Study305/04 was a parallel group comparison.

**Note(2):** As stated earlier, the term “recurrence” could be misleading, in that the Follow-Up detections confirmed as positive are not necessarily new lesions, but are possibly lesions missed during the Baseline exam. In fact, a rationale for the follow-up is that the combination White Light/Hexvix Blue Light cystoscopy should be thorough: not only should it detect lesions missed by White Light ; it should find all such lesions. If early follow-up cystoscopies detect as many “new” lesions in the Hexvix Arm as in the White Light Arm, then a claim for thoroughness for Hexvix cystoscopy becomes weak.

**Note(3):** Approximately 21% of the subjects in each arm were not “completers” for follow-up evaluations of the lesion recurrence endpoint. A subject is considered a “non-Completer” for various reasons, including loss to follow-up and absence of histology validation. The Sponsor imputed lesion recurrence to such subjects. Clearly, the imputation of recurrence to the 21% of subjects could seriously impact the primary statistics, especially if the percent of subjects with confirmed recurrences is comparable to the percent with imputed recurrences. For this reason the Reviewer has included an additional analysis, in which the non-completers were imputed recurrence rates consistent with completers. Thus, if the 79% of completers had recurrence rates of W% in the White light Arm and H% in the Hexvix Arm, then the 21% non-completers were imputed these respective rates.

**Note(4):** Once a positive detection is made on a subject, he/she exits the study as a completer.

**Table(9): Recurrence Endpoint Statistics**

	White Light Group ( N = 280 Subjects )		Hexvix Group ( N = 271 Subjects )	
	N	%	N	%
<b>Sponsor (Worst Case Imputation)</b>				
<b>All Recurrences</b>	<b>157</b>	<b>56%</b>	<b>128</b>	<b>47%</b>
<b>Validated Recurrences</b>	<b>97</b>	<b>35%</b>	<b>71</b>	<b>27%</b>
<b>Imputed Recurrences</b>	<b>60</b>	<b>21%</b>	<b>57</b>	<b>20%</b>
<b>Reviewer ( Extrapolation Imputation)</b>				
<b>All Recurrences</b>	<b>123</b>	<b>44%</b>	<b>90</b>	<b>33%</b>
<b>Validated Recurrences*</b>	<b>97</b>	<b>35%</b>	<b>71</b>	<b>26%</b>
<b>Imputed Recurrences</b>	<b>26</b>	<b>9%</b>	<b>19</b>	<b>7%</b>

**Discussion of Results:**

**Sponsor’s Statistics:** The Sponsor used the Cochran-Mantel-Haenszel Chi-Square Test with stratification by center to test if the recurrence rates in the two Arms were equal. The testing was done with alpha set at .01. The results are:

*White Light Arm Rate = 56% ; Hexvix Arm Rate = 47 % ; Difference = 9%  
CMH p-value ≈ .026 > .01*

*Since the stipulated alpha = .01, the Recurrence Endpoint criterion was not met.*

**Sponsor versus Reviewer Statistics:** The Reviewer calculated the recurrence rates restricted to completers and then extrapolated this rate to the non-completers. The results are:

*White Light Arm = 44% ; Hexvix Arm = 33% ; Difference = 11%*

In order to compare the Sponsor’s statistics ( Worst Case Imputation) to the Reviewer’s statistics ( Extrapolation Imputation) , a simpler approach will be taken:

(1): A 2-sided 99% CI for the difference White Light Rate – Hexvix Rate will be calculated under both imputations, using straightforward normal approximations.

(2): “Success” will consist in having the Lower Limit (LL) of the CI exceed zero.

Thus:

**Sponsor’s 2-sided 99% CI for Worst Case is ( -2% , 20%) LL = -2% ( Failure)**  
**Reviewer’s 2-sided 99% CI for Extrapolation is ( 0% , 22%) LL = 0% (Borderline)**

## Overall Conclusions

(1): The co-primary criteria for success in this single Study were:

(a): The White Light/Hexvix Blue Light combination cystoscopy should provide that at least 10% of the subjects have Ta/T1 detections under Blue light that were missed under White Light alone. This was achieved with the required level of statistical significance.

(b): Subjects who underwent the White Light/Hexvix Blue Light combination cystoscopy should have fewer early follow-up confirmed positive detections (recurrences) than did subjects who underwent White Light cystoscopy alone. This criterion was not achieved with the required level of statistical significance. These results were sensitive to the Worst Outcome Imputation; An alternative and exploratory scheme was more successful. However, the exploratory results are not intended as support for Recurrence Efficacy; the intention is only to highlight the sensitivity of results to Imputation schemes.

(2): Analyses stratified to continents ( US/Canada versus Europe) revealed that the overall subject level advantage for combination White Light/Hexvix Blue Light cystoscopy in detection of confirmed Ta/T1 lesions was not sustained for Europe. Since there was high correlation of continent with center size ( large centers in Europe , small centers in US/Canada ), a tentative conclusion is that centers with large enrollments are more successful with White Light detections of Ta/T1 than are centers with small enrollments, where the addition of Hexvix Blue Light offers an advantage.

(3): Analyses on lesion levels rather than on subject levels reveal that there is no overall detection advantage for Hexvix Blue Light over White Light. However, there is some evidence that Hexvix Blue Light is more successful in detecting CIS than is White Light, while White Light is more successful in detecting T2/T4 lesions.

(4): The inference drawn from the combined effect of all these analyses is that the overall results are not sufficiently robust.

#### 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

##### 4.1 Race, Gender and Age

Since over 90% of the subjects were Caucasian, no subset analyses were performed for race. The results for Gender and Age are presented and commented upon below.

**Table(10): Detection Results by Gender and Age**

<b>Detection Results by Gender</b>			
	<b># Subjects</b>	<b>Detected N</b>	<b>99% CI</b>
<b>Male</b>	<b>225</b> ( 79% of Subjects)	<b>35</b> ( 16% of 225)	<b>( 9.5% , 22%)</b>
<b>Female</b>	<b>61</b> (21% of Subjects )	<b>12</b> (20% of 61)	<b>( 7% , 33%)</b>
<b>Overall</b>	<b>286</b>	<b>47</b> (16% of 286)	<b>(11%, 22%)</b>
<b>Detection Results by Age</b>			
	<b># Subjects</b>	<b>Detected N</b>	<b>99% CI</b>
<b>≥ 65 Years</b>	<b>191</b> ( 67% of Subjects)	<b>33</b> (17% of 191)	<b>(10%, 24%)</b>
<b>&lt; 65 Years</b>	<b>95</b> (33% of Subjects)	<b>14</b> ( 15% of 95)	<b>(6%, 24%)</b>
	<b>286</b>	<b>47</b> (16% of 286)	<b>(11%, 22%)</b>

Comments: The rejection of the Null Hypothesis that the true percentage of Detections equal 10% at 0.01 level of significance translates informally into the criterion that the Lower Limit of the 2-sided 99% CI for the percentages of Detections have its lower limit above 10%. Note then that, although the point estimates in all 4 subsets above exceed 10%, it takes the full set of 286 subjects to achieve significance ( Lower limit = 11%).

**Table(11): Recurrence Results by Gender and Age**

<b>Recurrence Results by Gender</b>						
	<b>Hexvix Group</b>			<b>White Light Group</b>		
	<b># Subjects</b>	<b>Recurrent</b>		<b># Subjects</b>	<b>Recurrent</b>	<b>Difference And p-value</b>
<b>Male</b>	<b>212</b> (78% of Subjects)	<b>105</b> (50%)		<b>223</b> (80%)	<b>121</b> (54%)	<b>4%</b> <b>p-value ≈ .20</b>
<b>Female</b>	<b>59</b> (22% of Subjects)	<b>23*</b> (39%)		<b>57</b> (20%)	<b>36</b> (63%)	<b>24%</b>
<b>Overall</b>	<b>271</b>	<b>128</b> (47%)		<b>280</b>	<b>157</b> (56%)	<b>9%</b> <b>p-value ≈ .03</b>
<b>Recurrence Results by Age</b>						
	<b>Hexvix Group</b>			<b>White Light Group</b>		
	<b># Subjects</b>	<b>Recurrent</b>		<b># Subjects</b>	<b>Recurrent</b>	<b>Difference And p-value</b>
<b>&gt; 65 Years</b>	<b>168</b> (62% of Subjects)	<b>79</b> (47%)		<b>184</b> (66% of Subjects)	<b>106</b> (58%)	<b>11%</b>
<b>≤ 65 Years</b>	<b>103</b> (38% of Subjects)	<b>49</b> (48%)		<b>96</b> (34% of Subjects)	<b>51</b> (53%)	<b>5%</b>
<b>Overall</b>	<b>271</b>	<b>128</b> (47%)		<b>280</b>	<b>157</b> (56%)	<b>9%</b> <b>p-value ≈ .03</b>

**Comments:**

The most significant feature of this table is the breakdown of statistics by Gender. As reported earlier, the Recurrence Endpoint criterion was not met for the overall population, although the results came close:

P- value = .026 > .01 ( Alpha set for Rejection of the Null that the White Light Group had more recurrences than Hexvix Group=0.01.)

However, this “near miss” p-value is largely driven by the result of Hexvix versus White Light Recurrence differences for females who constituted only 22% of the study population. There is no evidence of reduction of Recurrences for males, who constituted 78% of the study population.

**4.2 Other Special/Subgroup Populations**

No other special populations or subgroups were considered in this application.

## **5. SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

See Sections 1.3 and 3.1 for detailed discussions of the statistical issues and collective evidence.

### **5.2 Conclusions and Recommendations**

Photocure submitted NDA 22555 on June 30 2009 , and the Agency directed that it be reviewed under priority status, with the PDUFA date set as December 30 2009. The submission included only one primary Phase III Study of the Sponsor's Test drug Hexvix - Study#305/04. This trial investigated the efficacy of a combination White Light/Hexvix Blue Light cystoscopy for detection of additional papillary bladder lesions, and for reduction of lesion "recurrence" (also called as "follow-up detection" in the clinical review to more appropriately convey the clinical interpretation of these data) when compared to standard White Light cystoscopy taken alone. The efficacy objective were, therefore, to show that a combination baseline White Light/Blue Light evaluation detected lesions missed by standard White Light cystoscopy, and that subsequent cystoscopies were less likely to present "new" (not detected previously) lesions (not to be interpreted as lesions newly formed not existing previously) than would a baseline standard White Light cystoscopy. The Study randomized subjects to a Hexvix Arm and a White Light Arm. Subjects in both arms underwent a baseline White Light cystoscopy for detection of bladder lesions ; subjects in the Hexvix Arm also underwent a Hexvix Blue Light examination during the same cystoscopy for detection of additional lesions. Subsequently, subjects in both arms were followed for nine months for detection of early lesion recurrence. The Hexvix Arm therefore played two roles: evaluation of additional lesion detections under combination White Light/Hexvix Blue Light cystoscopy, and evaluation of levels of lesion recurrence when compared to the recurrences in the Comparator White Light Arm. The protocol stipulated that the demonstration of Hexvix efficacy required not only statistically significantly improved detection, but also statistically significant reduced recurrence at 1% level of significance. The Sponsor met the improved Detection endpoint, but not the reduced recurrence endpoint. A special concern is that there is only one Phase III trial. Moreover, the poor performance on recurrence for males, who constitute 80% of the population, and the fact that improved true detection rates are accompanied by increased false detection rates, raises serious concerns regarding the adequacy of the results as support for the proposed detection indication.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22555	ORIG-1	PHOTOCURE ASA	HEXVIX

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