CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022555Orig1s000

MEDICAL REVIEW(S)

Medical Officer's Review of Complete Response

NDA: **22-555**
Product: Cysview (Hexaminolevulinate Hydrochloride)
Sponsor: Photocure ASA
Indication: Cysview Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnostic (PDD) system as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder in patients with known or suspected bladder cancer.
Reviewer: Scheldon Kress, MD, DMIP, ODE IV, CDER
Through: Dwaine Rieves, MD, Director, DMIP, ODE IV, CDER
Date: May 13, 2010

Introduction/Background

NDA 22-555 was submitted to the FDA June 30th 2009, for the following proposed indication, with the previously proposed proprietary name:

> "Hexvix Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnostic (PDD) system as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder in patients with known or suspected bladder cancer."

Following the review, FDA issued a Complete Response (CR) letter on 30 December 2009. Photocure submitted proposed responses to a number of the issues raised in FDA's letter in the Briefing Package dated 2 February 2010, and FDA and Photocure discussed these proposals in a Type B meeting 3 March 2010.

Based on the discussions at the 3 March 2010 Type B meeting, Photocure has prepared responses to all the issues raised by the FDA in the CR letter, and presented these in the current Complete Response submission. Module 3 documents which have been updated subsequent to information provided in the Complete Response are also included in the submission.

FDA has previously informed the applicant of the unacceptability of Hexvix as a proprietary name. Photocure has since submitted a new Request for Proprietary Name Review on 10 February 2010 and has been anticipating that a new proprietary name for Hexaminolevulinate Hydrochloride, CYSVIEW, might be approved and will be available in time for approval of NDA 22-555. Therefore in this resubmission, although the name

"Hexvix" has been maintained in updated Module 3 documents to provide consistency in the nomenclature of Module 3 of NDA 22-555, the name "Cysview" has been implemented in the proposed Package Insert, labels and carton. .

During the filing review of the current application, FDA has determined that it represents a Type 1 (2 month review clock) resubmission of the New Drug Application 22-555

Discussion

The Sponsor has provided responses related to the issues raised in the Complete Response letter and the FDA's respondence is summarized here.

A. Concerns Adequately Addressed by Sponsor

The following Sponsor's responses have adequately addressed the Agency's concerns and are acceptable.

1. Photocure has revised the reconstitution and preparation process for Hexaminolevulinate Hydrochloride Solution to minimize the risk of medication errors and sharps-injury to the healthcare provider. The revised procedure is described in the proposed Package Insert with easy to understand diagrams.

2. Photocure has adequately addressed issues related to choice of urethral catheters to be used for instillation and for provision of a Luer-Lock catheter adaptor in the marketed kit carton.

3. Photocure has evaluated the compatibility of Hexaminolevulinate Hydrochloride with the inner wall of catheters and the adapter lumens.

4. Photocure has clarified the instructions regarding removal of the catheter post instillation and the handling of patients who are unable to retain the Hexaminolevulinate Hydrochloride solution in the bladder for a full hour. Adequate clinical data were provided to support the proposed labeling provisions.

5. In Photocure's response the following additional instructions were provided: "Practically, the patient needs to be able to stand, sit and move about during the hour between instillation and the start of the cystoscopic procedure." This reviewer recommends adding this information to the revised Package Insert.

6. In Photocure's response the following additional information was provided: "T2 tumors have a tendency to be necrotic on the surface. As necrotic cells will not absorb Hexaminolevulinate Hydrochloride, no fluorescence will be detected from such a lesion under blue light." This reviewer recommends adding this information to the revised Package Insert.

7. Photocure has provided more details within the revised Package Insert regarding the instillation and evacuation procedures and perineal care when administering Hexaminolevulinate Hydrochloride into patients' bladders.

8. Photocure clarified that the content, performance and record keeping of cystoscopic examinations with an added Hexaminolevulinate Hydrochloride fluorescence blue light component is unchanged from the diagnostic procedure employed routinely by trained urologists for detection of bladder cancer in surgical suites and therefore, additional detailed instructions of cystoscopic examination techniques are considered unnecessary.

9. Photocure clarified that "switching between white and blue light" was not a component of any clinical study and has not been proposed by the sponsor. Instead, after the TURB, the physician is instructed to check for complete resection under white light and blue light. This check is included to ensure that the physician has successfully been able to resect all the lesions that were detected under both white light and blue light cystoscopy, and is in accordance with the procedure described in the clinical study PC B305/04 protocol.

10. Photocure clarified that "bladder mapping" used to describe the documentation of suspicious bladder lesions for later biopsy and resection varies by individual healthcare institutions, each with its own standard operating procedures and preferred practices for the documentation of findings. Urologists perform this routine diagnostic procedure in compliance with their formal training, instruction and experience. As long as an efficient "mapping procedure" is being utilized, there may not be a need to adjust or change these "mapping procedures" for use during Hexaminolevulinate Hydrochloride Fluorescence blue light cystoscopy as compared to mapping used during standard white light cystoscopy alone.

11. Photocure is in agreement with the agency to delete the citations related to the "recurrence reduction" outcomes.

Even though in Europe the use of Hexaminolevulinate Hydrochloride is not restricted to single usage, Photocure has placed strong language in the proposed Package Insert (b) (4) This satisfies the Agency's concern regarding the lack of data regarding the safety of repeated administration of this product.

B. Concerns Requiring Further Discussion

The Sponsor's responses to the following issues/concerns require further discussion and are reviewed here:

1. Evaluation of potential for repetitive administration of product

The FDA requested information regarding the Sponsor's plans for subsequent clinical studies that examine the safety and efficacy of repetitive administration of Hexaminolevulinate Hydrochloride.

Sponsor's proposal to address the safety of repetitive administration
The sponsor states that Hexaminolevulinate Hydrochloride has been marketed since 2006 and currently more than (b) (4) cystoscopic examinations have been performed using Hexaminolevulinate Hydrochloride in Europe. The sponsor further states that, as will be the case in the US, Hexaminolevulinate Hydrochloride is not used in outpatient cystoscopic examinations in Europe.

In Europe, Hexaminolevulinate Hydrochloride ("Hexvix") is not restricted to single use, and repeat use of the product is not unusual. Photocure cites data from (b) (4) to indicate that a substantial number of patients in Europe are likely to have received Hexaminolevulinate Hydrochloride more than once and states that no safety issues have been reported to Photocure as a result of repeat use of Hexaminolevulinate Hydrochloride in the post marketing safety follow-up.

Photocure proposes that the most appropriate way to obtain safety data on repeat use of Hexaminolevulinate Hydrochloride is to establish a voluntary registry and invite all Hexaminolevulinate Hydrochloride user facilities in Europe to participate. Photocure proposes to establish an online registry in Europe, where more than (b) (4) cystoscopic examinations have already been performed using Hexaminolevulinate Hydrochloride. The data that would be collected would focus on potential safety issues related to the repeat administration of Hexaminolevulinate Hydrochloride.

Photocure proposes that the following data be collected: basic demographic information of the patient, (age and gender, any known allergies and if so, which allergies) the dates for the initial and the repeated Hexaminolevulinate Hydrochloride administrations, type of examination (cystoscopy, cystoscopy and biopsy, or cystoscopy and TURB), BCG and/or chemotherapy since last administration of Hexaminolevulinate Hydrochloride, as well as any adverse event that is considered to be related to Hexaminolevulinate Hydrochloride.

According to Photocure, given the recurrence rates and the intended use of Hexaminolevulinate Hydrochloride in combination with the operating room cystoscopic examinations, it would be take several years to obtain data on repeat use of Hexaminolevulinate Hydrochloride in a prospective clinical trial where the design would reflect the intended use of Hexaminolevulinate Hydrochloride. The applicant states the following: "If 100 patients were enrolled in a clinical trial with initial diagnosis of bladder cancer, 15-61 of these would be expected to have recurrence of their bladder cancer and have an indication for a second administration of Hexaminolevulinate Hydrochloride within one year after initial diagnosis. Therefore to perform a controlled clinical study to obtain data on repeat use of Cysview in a reasonable number of patients

would take several years, and a registry as described above is considered the most timely and appropriate way to obtain the requested data".

Sponsor's proposal to address the efficacy of repetitive administration

Photocure further argues that whereas there might be potential safety issues with repeat use of the drug, there would be no reason to expect that the efficacy of Hexaminolevulinate Hydrochloride will differ if used for a follow-up cystoscopic examination conducted as part of routine surveilance monitoring in patients having been treated for bladder cancer or suspected of bladder cancer recurrence. Based on current clinical practice such monitoring would limit the interval between repeat uses to no more frequent than 3 months.

Reviewer's comments on the sponsor's proposals

This reviewer agrees that taking advantage of data from (b) (4) patients with prior Cysview exposure in Europe could provide information regarding the safety and efficacy of repeat administration in a more reasonable period of time. To obtain meaningful data from the proposed voluntary registry, we offer the following recommendations:

Safety Issues

1) Assessment of adverse events occurring after each repeated Cysview administration should specifically include: immediate monitoring for such adverse events as allergic/hypersensitivity reactions and subsequent pain, urinary infections and dysfunction, and other urologic complications.
2) Follow-up of cystoscopy #2 should include another two cystoscopic examinations (#3 and #4, every 3 months, respectively) with querying for post-procedure symptoms and bladder evaluation for mucosal changes including scarring and decreased bladder volume.

Efficacy Issues

Assessment of efficacy reliability during repeat administration should include clinical assessment of maintenance of added value of Cysview and blue light cystoscopy to detect cancerous bladder lesions not detectable by white light cystoscopy and the demonstration of absence of any negative impact on ability to visualize the bladder during repeat examination, therefore providing reassurance that the rates of false detection and failure of detection do not rise with the repeat use. Such efficacy evaluation could be particularly addressed to carcinoma-in-situ detection which appears to be a particularly relevant area for potential clinical usefulness of this diagnostic technology.

Study design and size

The sponsor will have to propose a pre-specified minimum number of patients which will be available for the follow-up cystoscopic examinations. A clinical trial rather than a registry might be more appropriate and meaningful for the assessments outlined above.

2. Unique procedural (training) manual

It remains of utmost importance that all urologists planning to add Cysview blue light cystoscopy into their practices be thoroughly trained and familiarized with the materials contained in the Package Insert and the Physician Training Manual, as well as all the applicable device labeling. The sponsor has proposed a training manual and included it in the Meeting Request submission as an amendment to the NDA in February, 2010, with the electronic link provided in the current submission. The review of the manual found its content to be acceptable and consistent with the drug label. The information included in the manual is supplemental to the information provided in the label for the conduct of a cystoscopic examination using Cysview and blue light.

3. Comment in label: (b) (4)

FDA comment based on the information provided by CDRH in the e-mail of 4/30/10:

(b) (4) the basis for (b) (4) blue light exposure - Based on the mode of action of Cysview, it is expected that prolonged exposure to blue light may cause additional cellular damage in bladder mucosa tissue, although adequate evaluation has not been available. In study PC B305/04, the average total minutes (min, max) of exposure to blue light was 5.03 ± 3.111 (0.7, 11.4) min, exposure to white light was 13.58 ± 8.429 (1.2, 35.9) min . This is probably the basis for the recommended (b) (4) exposure to blue light. Following labeling revision is suggested: "Adverse effects from prolonged exposure to blue light has not been adequately evaluated, although prolonged exposure to blue light may increase risk of damage in normal bladder mucosa. The average total time of exposure to blue light from current PDD system was 5.03 ± 3.111 minutes in clinical study, with minimum of 0.7 minutes and maximum of 11.4 minutes."

Proposed Package Insert

Photocure has up-dated and revised the proposed Package Insert. This Reviewer has contributed further revisions to the Package Insert which is still being finalized at the present time.

Recommendation

Based on safety and efficacy assessment during the first review cycle and the current review of the sponsor's response to the December 30, 2009 CR letter, this reviewer recommends approval of Cysview (Hexaminolevulinate Hydrochloride) for the proposed indication.

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

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/s/

SCHELDON KRESS
05/13/2010

ALEXANDER GOROVETS
05/14/2010
Clinical Team Leader concurs with the Primary Clinical Reviewer's conclusions and recommendations.

CLINICAL REVIEW

Application Type	NDA
Application Number	22-555
Submit Date	June 30, 2009
Received Date	June 30, 2009
PDUFA Goal Date	December 30, 2009
Division / Office	DMIHP/OODP
Reviewer Name	Scheldon Kress, M.D.
Review Completion Date	November 30, 2009
Established Name	Hexaminolevulinate HCl for Intravesical Solution
(Proposed) Trade Name	Hexvix®
Pharmacological Class	Optical Imaging Agent
Applicant	Photocure ASA, Norway
Priority Designation	P
Formulation	100 mg Powder & 50 ml Diluent
Dosing Regimen	Bladder Instillation via catheter 50mL 8 mM (2 mg/ml) solution
Indication	Detection of papillary bladder cancer - fluoresces red with blue light (b) (4)-450 nm Wave Length)
Intended Population	Suspected bladder cancer

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the clinical review of study design, conduct and the analysis of study results, substantial evidence of effectiveness of Hexvix plus blue light cystoscopy has been demonstrated for detection of non-muscle invasive papillary cancer of the bladder as an adjunct to white-light cystoscopy. Hexvix is instilled into the bladder prior to white-light and blue-light cystoscopy. The application for Hexvix - a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder is approvable. Whereas this is a combination product, approval is pending the current review by CDRH of PMA P050027 for the Karl Storz Photodynamic Diagnosis (PDD) system.

1.2 Risk Benefit Assessment

Combining Hexvix blue light (BL) cystoscopy with standard white light (WL) cystoscopy demonstrated a significant and clinically relevant improvement in detecting Ta or T1 tumors over standard WL cystoscopy alone. Because Hexvix BL cystoscopy is intended as an add-on procedure to WL cystoscopy to improve the early detection of papillary bladder cancer, its benefit is as an aid in more effectively detecting Ta and T1 tumors. The detection of additional papillary tumors provides a method to identify the disease at an earlier stage, enabling a more precise and complete resection.

The clinical safety of Hexvix cystoscopy was evaluated in 1,324 patients in clinical studies and from 57,000 patients exposed post-marketing in Europe. On the basis of the results presented in this summary and on 5+ year postmarketing pharmacovigilance in more than 57,000 patients, Hexvix cystoscopy has been shown to be safe and well tolerated and unlikely to contribute appreciably to the adverse events (AEs) seen with current diagnostic procedures for bladder cancer. The incidence, nature, and severity of AEs and serious AEs (SAEs) were similar in both the Hexvix-cystoscopy and the WL cystoscopy study groups. During Hexvix postmarketing surveillance period, an isolated SAE of anaphylactic shock has been reported and Hexvix may have a potential risk for hypersensitivity reactions.

Numerous published data also show that no serious adverse effects with photodynamic cystoscopy have been reported other than those seen with WL cystoscopy. Furthermore, AEs that were observed were expected, based on previous experience with WL cystoscopy and transurethral resection of bladder (TURB) procedures.

The investigator considered most of the AEs due to extraneous causes, such as disease, concomitant medications, procedures, or environment (i.e., as unrelated to Hexvix).

More than 70% of investigators in pivotal Study 305 found Hexvix cystoscopy as an add-on procedure to WL cystoscopy to be useful in diagnosing bladder tumors, and more than half of investigators found Hexvix cystoscopy to be useful for deciding further patient management.

Benefits of Hexvix blue light cystoscopy as an adjunct to white light cystoscopy in patients with known or suspected bladder cancer include the following:

• It is safe and well tolerated. The safety profile is similar in both the Hexvix-cystoscopy and the white light study groups.
• It is an effective additive diagnostic method for the detection of non-muscular invasive bladder tumors.
• It enables a more complete early removal of superficial bladder tumors.
• Hexvix cystoscopy is easy to implement as a complementary diagnostic method to white light cystoscopy alone.

Risks of Hexvix cystoscopy include the following:

• When lesions are detected by blue light cystoscopy alone, the false-positive detection rate is slightly higher than when detected by white light cystoscopy alone.
• Biopsy/resection with white light cystoscopy prior to blue light cystoscopy, inflammation and instillation of BCG or chemotherapy have the potential to increase the false-positive detection rate.
• Performance of blue light cystoscopy without white light cystoscopy should not be done as it will result in the missing of pathologic lesions.
• Hexvix may have the potential of causing hypersensitivity reactions and rarely anaphylaxis.
• The safety of repeated instillation of Hexvix and repeated exposure to blue light cystoscopy on bladder epithelial cells has not been fully evaluated.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Based on the review of the data provided in this application, there are no indications for recommending a Postmarket Risk Management Evaluation and Migration strategy.

1.4 Recommendations for Postmarket Requirements and Commitments

Based on the review of the data provided in this application, there are no indications for recommending Postmarket Risk requirements and commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Hexvix is a diagnostic Imaging agent with fluorescing properties when illuminated by blue light, used during cystoscopic examination of the urinary bladder as an adjunct to standard white light cystoscopy to improve detection of bladder cancer. PhotoCure developed hexaminolevulinate hydrochloride (HAL, P-1206), the active moiety in Hexvix, for detection of bladder cancer. HAL is an ester of the endogenous early precursor in the biosynthesis of heme, 5-aminolevulinic acid (ALA). The rationale for developing Hexvix is based on its ability to induce the formation of fluorescent porphyrins (PAP) in the urothelium when instilled in the bladder, and its apparent selectivity for malignant and pre-malignant tissues.

The drug is supplied as a kit with 2 components: 100 mg of freeze-dried Hexyl aminolevulinate (HAL) hydrochloride, the Powder, and 50 mL Solvent for Hexvix solution for intravesical use. Hexvix is formulated as a powdered solution for intravesical use. It is reconstituted (b) (4) before instillation in the bladder (administration required within 24 hours of reconstitution).The powder contains 100 mg hexaminolevulinate hydrochloride, corresponding to 85 mg of the active moiety HAL. Dissolution in 50 mL Solvent for Hexvix provides an 8 mM (1.7 mg/mL) solution of HAL for intravesical instillation. .

In all phase 3 clinical trials, Hexvix 8 mM solution (50 mL) was instilled into the bladder via catheterization and retained for 1 hour (per protocol). Following voiding, all protocols called for the initiation of anesthesia and white light cystoscopic examination in conjunction with blue light illumination within thirty minutes. Additional filters in this special cystoscope light source allow examination with both white and blue light. Following Hexvix instillation, malignant tissues fluoresce red when illuminated under blue light ((b) (4) -450 nm wavelength).

Hexvix was first approved in 2004 in Sweden with the following indication: “Detection of bladder cancer, such as carcinoma in situ, in patients with known bladder cancer or high suspicion of bladder cancer”, based on screening cystoscopy or positive urine cytology. Subsequently, Hexvix was approved in a total 28 countries in Europe plus Korea. Blue

light fluorescence cystoscopy should be used as an adjunct to standard white light cystoscopy, as a guide for taking biopsies.

Photodynamic blue light cystoscopy is performed with Karl Storz Photodynamic Diagnosis (PDD) system. For this combined examination The Karl Storz Photodynamic Diagnosis (PDD) system with D-light C as the light source has been used in the clinical studies with Hexvix and consists of a rigid Hopkins® II telescope with a camera system. This PDD system has reportedly been safely used in the European Union since 1995. This PDD system is not approved for use in the US but the premarket approval application (PMA 050027) was submitted in parallel to this NDA submission.

FDA's review of this combination product requires two marketing applications and each is ongoing, one for Hexvix (CDER – the imaging agent) and the Karl Storz Photodynamic Diagnosis (PDD) system (CDRH - the light source). Both submissions rely on the clinical data provided in the NDA.

2.2 Tables of Currently Available Treatments for Proposed Indications

The currently available procedure, white light cystoscopy, is the standard diagnostic procedure for assessing disorders of the lower urinary tract.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in Hexvix is not marketed in the United States.

2.4 Important Safety Issues with Consideration to Related Drugs

No important issues are known with pharmacologically related products. Conceivably, other intravesical products (such as chemotherapeutic agents and vaccines) may alter Hexvix diagnostic utility. For this reason, patients with prior BCG or chemotherapy were excluded from clinical trials. These concerns are not addressed in this submission, but will be addressed in the final label.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The primary focus of the clinical development program for Hexvix was to demonstrate the additional value of Hexvix photo-fluorescent cystoscopy when compared to standard white light cystoscopy in the detection of bladder cancer. In general, two major bladder cancer detection indications were sought: one for the detection of CIS and the other for detection of non-muscle invasive carcinoma.

The clinical development program for Hexvix cystoscopy began in 1997 with an exploratory feasibility and dose-finding study (Study 001) and a systemic absorption of radiolabeled HAL study (Study 103). In the radiolabeled HAL study, 7% of the radioisotope instilled into the bladder appeared within the blood following the intravesical administration. This observation suggests that some systemic absorption may occur following Hexvix instillation into the bladder.

A Phase 2 study (Study 201) of a small number of patients provided dose-response information. Three major, controlled phase 3 Studies (Studies 301, 302, and 303) were conducted to support the efficacy of Hexvix cystoscopy for the detection of CIS. A single major phase 3 study in 28 centers addressed the non-muscle invasive papillary cancer detection goal, Study 305, followed by Study 304, a smaller sample size, two-center study intended to supply supportive data. Major findings from the phase 3 studies that assessed the potential CIS detection indication are also cited as supportive data.

Following submission of an investigational new drug application in 2001, the sponsor conducted clinical studies directed toward two major bladder cancer detection indications, one for carcinoma in situ (or CIS) and the other for papillary bladder cancer. During the development process three phase 3 studies addressed the CIS indication and a single major phase 3 study addressed the papillary bladder cancer indication. I will refer to this single study as Study 305. A special protocol assessment for study 305 was submitted in 2003 and FDA provided advice regarding the design of this study with the understanding that the sponsor intended data from this single study to confirm efficacy and safety. The sponsor incorporated FDA's advice into the final clinical protocol. In 2005, the sponsor completed the CIS program and submitted a new drug application specifically for the use of Hexvix in the detection of CIS; at that time the development program for the papillary cancer indication was on-going.

On 30 June 2005, a New Drug Application (b) (4) for Hexvix cystoscopy was submitted to the Food and Drug Administration (FDA) with data to support a different indication for Hexvix: "the detection of carcinoma in situ (CIS) in the bladder by using blue-light cystoscopy as an adjunct to WL cystoscopy in patients with known or suspected bladder cancer." In July 2005, PMA 050027 (Karl Storz PDD system) was submitted to CDRH by Karl Storz Endoscopy America subsequent to Photocure's submission of NDA (b) (4) (Hexvix) to CDER. The proposed indication for the combined use of the device and the drug was for "detection of carcinoma in situ (CIS)". NDA (b) (4) and PMA 050027 were both supported by data generated during the use of Karl Storz PDD system using D-Light as light source. On 13th of November 2006, PMA 050027 was amended to introduce D-Light C as the light source.

FDA's review of the CIS detection NDA found concerns with the application mainly related to the inability to verify the thoroughness of white light cystoscopic examinations and inconsistencies in pathology diagnoses between the investigational sites and central pathology facility. These deficiencies precluded approval of the application and FDA requested additional studies for the CIS. Subsequently, the sponsor completed the papillary cancer development program and this papillary cancer detection indication is the subject of this NDA which was submitted earlier this year.

In parallel with the clinical development program for CIS, Photocure was investigating the efficacy of Hexvix for detecting other lesions commonly found in patients with bladder cancer. On 19 April 2006, the FDA issued a non-approvable action letter regarding NDA (b) (4) stating that additional clinical studies were needed to verify the diagnostic efficacy of the product for CIS. After discussions with Photocure (26 October 2006, 15 February 2007, 16 April 2008, 29 January 2009 and 01 April 2009), the FDA agreed that data from Study 305, a study initiated in 2005 to investigate the detection of papillary tumors with Hexvix, could be utilized to support an NDA with a modified indication. The current application (NDA 22-555) relies upon the data from Study 305.

Trial 305 was subject to a special protocol assessment; the special protocol assessment was submitted on 12 January 2004 (Investigational New Drug Application [IND] 51,224, Serial Number [SN] 0049), and the protocol was finalized 02 June 2004. The statistical analysis plan (SAP) for Study 305 was discussed with the FDA in a meeting on 25 November 2003, after being described in meeting package dated 11 November 2003 (IND 51,224, SN 046), and acknowledged in FDA minutes dated 25 November 2003. The final version of the SAP was discussed at a Type C meeting held by teleconference on 15 February 2007, with supporting meeting request and background information, dated 07 December 2006 (IND 51,224, SN 0069), and subsequent FDA meeting minutes dated 15 March 2007 and 07 May 2007.

After the not approvable letter for NDA (b) (4) was received, Photocure had discussions with the FDA, and a strategy for addressing the clinical comments of the not approvable letter was agreed upon. The following two measures were implemented in the clinical study protocol for Study 305 to address the clinical comments in the not approvable letter issued to NDA (b) (4):

1. Increased rigor and standardization in the pathology diagnosis were ensured by the design of the central pathology panel read. This central pathology panel read was described in the Type C meeting request (IND 51, 224, SN 0069), and agreed upon with the FDA at the teleconference 15 February 2007 (refer to the FDA meeting minutes dated 15 March 2007 and 07 May 2007). The procedure for the central pathology panel read was submitted to the IND on 03 December 2007 (IND 51,224, SN 0081). (See **Figure 3**)

2. The quality and thoroughness of the WL cystoscopy examination in Study 305, were documented in the briefing package sent to the FDA and dated 14 March 2008 (IND 51,224, SN 0084), with the FDA's response dated 16 April 2008.

This modified indication was for "Hexvix is as an adjunct to WL cystoscopy in the detection of non–muscle invasive papillary cancer of the bladder." Data in support of this detection indication in the present NDA are obtained primarily from a controlled, randomized, open label Phase 3, multicenter study (28) in 814 patients with papillary bladder cancer (Study 305) and a supportive recurrence reduction randomized, Phase 3, two-center study in 233 patients suspected of having non–muscle invasive bladder cancer (Study 304). The sponsor suggested that additional supportive efficacy data were provided from the 366 subjects with papillary bladder cancer in Studies 301, 302, and 303, which are studies submitted in support of the CIS indication in (b) (4). **Table 26** displays the results from these exploratory supportive studies for detection of Ta and T1 bladder tumors. During the review of NDA (b) (4) inconsistencies were revealed in the pathologic readings from Studies 302 and 303. Whereas the overall clinical data did not provide verifiable evidence of efficacy, the efficacy results based on these earlier studies were not re-reviewed.

As a follow-up to the "not approvable" letter to PMA 050027, issued by CDRH on 15 February, 2007, Karl Storz and Photocure have provided data to address CDRH's safety concerns. The most recent relevant data provided to CDRH (September 25, 2009) was intended to address all outstanding safety concerns.

PhotoCure requested Priority Review Designation for this submission based on the following information: Bladder cancer is the forth most common form of cancer affecting men, and eight most common cancer among women. Hexvix photodynamic blue light cystoscopy is an innovative product that may significantly improve the detection of papillary bladder cancer when utilized as an adjuvant to white light cystoscopy. Missing residual tumor increases the probability of early recurrence/progression and is associated with an increased risk of morbidity and death. If the sponsor can demonstrate that Hexvix can significantly improve the ability to detect cancerous bladder tumors present during a cystoscopic examination without adding significantly to the risk of the procedure, then Hexvix photodynamic blue light cystoscopy would be a significant improvement in the diagnosis and management of bladder cancers. Therefore, Priority Review Designation was granted.

2.6 Other Relevant Background Information

Bladder cancer affects primarily older people; nearly 90% of people with bladder cancer are over the age of 55 years, and 67% are over the age of 65 years. Men are four times more likely to be affected than women, and whites are diagnosed with bladder cancer almost twice as often as blacks or Hispanics. The etiology of bladder cancer appears to

involve multiple factors, with exogenous environmental factors as well as endogenous molecular factors playing possible roles.

Of urothelial bladder tumors, 90% to 95% are transitional cell carcinoma, usually papillary and multicentric, while squamous cell carcinoma accounts for 5% and adenocarcinoma accounts for 2%. Transitional cell carcinoma can be either non-muscle invasive (pathologic Stages CIS (Tis), Ta and T1) or muscle invasive (pathologic Stages T2 to T4). In patients with the diagnosis of bladder cancer, about 70% present initially as non-muscle-invasive bladder tumors, and the remainder as invasive cancer.

Among the non-muscle invasive transitional cell carcinoma, 70% present as papillary tumors (stage Ta) confined to the bladder mucosa. A total of 5% to 10% of the patients present with carcinoma in situ (CIS, stage Tis), which are non-exophytic or "flat" lesions that are frequently multifocal and can occur alone or in conjunction with papillary lesions. CIS lesions are, by definition high grade, and are associated with high recurrence rates and a high likelihood of progression. Approximately 20% of non-muscle-invasive transitional cell carcinomas have invaded the underlying connective tissue (lamina propria), (stage T1). These tumors have a high rate of recurrence and progression, and eventually become invasive in 30% of cases.

Treatment is dependent upon pathologic examination and tumor staging. CIS lesions are treated with TURB and BCG instillation, Ta and T1 lesions are treated by TURB and T2-T4 lesions are treated by bladder resection. All patients with bladder cancer have routine follow-up cystoscopies approximately every three months initially. Therefore, Ta and T1 papillary lesions are the ideal bladder cancer patients for this type of study.

Important endpoints in the natural history of bladder cancer include recurrence, progression and survival. Progression is defined as the development of higher grade tumors with muscle invasion or metastatic disease, and is associated with an increased risk of death. The probability of progression at one year ranges from about 1% to 17% and from 1% to 45% at 5 years. Recurrence defined as appearance of tumors of the same stage and grade as the primary tumor is common. Residual tumor after incomplete resection, microsatellites missed during initial transurethral resection of the bladder (TURB) or true recurrence can be the cause of early bladder cancer recurrence. Depending on a patient's characteristics after TURB the probability of recurrence at one year ranges from about 15% to 61% and from 31% to 78% at 5 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Only clinical sites from Study 305 were inspected by the FDA. For the three study sites inspected, sufficient documentation was obtained to assure that the subjects audited did exist, study eligibility criteria were fulfilled, participants received assigned study medications and adverse events were reported. Primary endpoints and secondary endpoints were captured in accordance with protocol requirements.

3.2 Compliance with Good Clinical Practices

Available data provide reasonable assurance that all clinical studies were conducted in compliance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, and the applicable regulatory agency requirements, including Title 21 of the Code of Federal Regulations, Parts 50, 56, and 312, and International Conference on Harmonization E6.

3.3 Financial Disclosures

Financial disclosure information was obtained from all investigators. One hundred and fifty-two clinical investigators participated in Study 305 world-wide and four clinical investigators in Study 304 in Denmark. Only (b) (6) had proprietary financial interest in the product under investigation.

(b) (6) hospital contributed 75% of the patients for Study 304, the supportive "recurrence trial" in this application. However, this trial did not demonstrate efficacy. (b) (6) hospital did not participate in clinical trials that supported this application. Details of the two clinical investigators who disclosed financial arrangements and proprietary interests follow:

(b) (6) is one of seven inventors on a patent application, secondary to Photocure's basic patent on the use of ALA esters in photodiagnosis and photodynamic therapy. The patent application has been licensed to Photocure ASA against a minor royalty payment to (b) (6) institution.

(b) (6) is one of nineteen centers from eight countries in Europe participating in Study 301. (b) (6) contributed with 15 out of 286 enrolled patients. The efficacy results for the main parameters are presented by country in the clinical study report, and (b) (6) represents the only centre in Switzerland.

Study 301 is not a pivotal Phase 3 study in NDA 22-555. Study 201 was a dose finding confirmatory Phase 2 study. The primary objectives were to determine the sensitivity and specificity of Hexvix blue light cystoscopy in patients with bladder carcinoma. (b) (6) is one of four centers in four countries in Europe. (b) (6) contributed with 18 out of 54 enrolled patients.

(b) (6) was the principal investigator for the clinical study 304. Study 304 was ongoing from 2005 to 2008. (b) (6) has received honoraria for consultancy work and for speaking assignments from Photocure that in total exceeds 25,000 USD for this period. (b) (6) was one of two centers participating in this study. (b) (6) contributed with 175 out of 233 patients in this study (75% of patients).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

CMC aspects do not directly relate to the clinical data

4.2 Clinical Microbiology

The drug product is an (b) (4) lyophilized powder for injection in a glass vial. The drug product is packaged with an aqueous solvent (b) (4) in either a glass vial or a polypropylene (b) (4) vial. Updated information was provided as needed, (b) (4).

4.3 Preclinical Pharmacology/Toxicology

The nonclinical testing program consisted of primary and secondary pharmacology studies, safety pharmacology studies, pharmacokinetic studies, and a battery of toxicology studies. No signs of systemic toxicity have been observed after repeated instillations of hexaminolevulinate in animals.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

HAL (Hexyl 5-aminolevulinic acid) is an ester of the endogenous early precursor in the biosynthesis of heme, 5-aminolevulinic acid (ALA). The rationale for developing Hexvix is based on its apparent selectivity for malignant and pre-malignant tissue and its ability when instilled in the bladder to induce the formation of fluorescent porphyrins (PAP) in malignant urothelial lesions that fluoresce red under blue light.

(b) (4)

4.4.2 Pharmacodynamics

In Study 001, the feasibility of Hexvix fluorescence cystoscopy was first assessed in humans. Hexvix 4, 8 and 16 mM solutions were tested in 25 patients with bladder cancer using different instillation times. The effects of time and drug dose on the formation of photoactive porphyrin (PAP)-fluorescence were studied with an optical fiber-based spectrofluorometer. Neither local nor systemic side effects were observed. All conditions yielded preferential porphyrin accumulation in neoplastic tissue with a high precision of demarcation with the red fluorescence. There was a bell-shaped dose relationship using two-hour instillation, Hexvix 8 mM giving a higher porphyrin-fluorescence compared with both 4 and 16 mM concentrations. There was also a correlation between instillation time and increasing porphyrin fluorescence intensity. However, using a two-hour instillation and a two-hour rest after bladder evacuation before illumination (2+2 regime,) proved to induce higher fluorescence intensity than a four-hour instillation time. In the major clinical studies, cystoscopy was performed after one hour.

Samples of normal human bladder were taken from four patients undergoing radical cystectomy in order to determine the penetration of Hexvix through the bladder wall. Measurement of PAP-fluorescence showed that fluorescence was observed mainly in the urothelium with little in connective tissue and no detectable amounts in muscle. The efficacy of Hexvix 8 mM was investigated using a 30-60 minute instillation before illumination in 27 patients with bladder cancer. There were no reports of adverse reactions. Negative and positive predictive values were 92% and 68% respectively.

4.4.3 Pharmacokinetics

One pharmacokinetic (PK) study was performed to determine absolute bioavailability of Hexvix. Study 103 showed that following intravenous administration in plasma, [^{14}C]-labeled Hexvix displays biphasic elimination, with an initial elimination half-life of 39 minutes, followed by a terminal half-life of approximately 76 hours. However, the systemic exposure to HAL hydrochloride after intravesical administration for one hour to healthy volunteer was low, with a mean bioavailability of 7% and a 90% confidence interval of 5-10%.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary focus of the clinical development program for Hexvix was to demonstrate the additional value of Hexvix fluorescence cystoscopy when compared to standard white light cystoscopy in the detection of papillary bladder cancer and on the impact of the potentially improved tumor detection on the treatment of the patient. All trials were open label. **Table 1** summarizes the clinical development program.

The clinical development program for Hexvix cystoscopy began in 1997 with an exploratory feasibility and dose-finding study (Study 001) and a systemic absorption of radiolabeled HAL study (Study 101). A controlled Phase 2 study, Study 201, of a small number of patients provided dose-confirmatory information. Three controlled phase 3 Studies, 301, 302, and 303, comparing white light cystoscopy with Hexvix ("blue light" fluorescence) cystoscopy to white light cystoscopy alone were conducted to support the efficacy of Hexvix cystoscopy for the detection of CIS. Data from these three phase 3 Studies were submitted to support NDA (b) (4) However, this application was not approved (b) (4).

On 19 April 2006, the FDA sent a regulatory action letter regarding NDA (b) (4) that stated that additional clinical studies were needed to verify the diagnostic efficacy of the product for CIS. At that time, there were two ongoing Phase 3 studies of Hexvix being conducted by Photocure: Study 305 and Study 304, both investigating Hexvix cystoscopy for papillary lesion detection and the impact of Hexvix cystoscopy on tumor recurrence rates. After interactions between the FDA and Photocure (26 October 2006, 15 February 2007, 16 April 2008, 29 January 2009, and 1 April 2009), it was agreed that Study 305 could be used to support a new NDA with a modified indication.

This NDA focuses on the data from the registration study, Study 305, and the supportive study, Study 304. Efficacy data from Study 305 are presented to support the detection indication and data from Study 304 are presented separately as supportive data.

Photocure proposed that the data provide sufficient evidence of efficacy to support the following indication for Hexvix cystoscopy:

> "Hexvix Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnostic (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder in patients with known or suspected bladder cancer"

Studies 301, 303, and 304 were conducted in Europe, Study 302 was conducted in the United States and Canada, and Study 305 was conducted in the United States, Canada, and Europe.

Table 1 : Clinical Development Program for HEXVIX (All OL)

Trial #	Patients n	Primary Endpoint / Analysis
305	814	Compare proportion additional confirmed papillary bladder cancers detected with BL compared with WL cystoscopy & any recurrences following TURB (patient level)
304	233	Compare proportion of patients with recurrences of superficial bladder cancer following BL TURB and WL TURB (patient level)
303	162	Compare intended patient management – whether BL cysto added valuable management information
302	311	Compare proportion of patients with additional confirmed CIS with BL but not found with WL cystoscopy (patient level)
301	286	Compare proportion of additional confirmed CIS lesions with BL compared with WL cystoscopy (lesion level)
201	52	Dose-confirmatory
103	8	Systemic absorption of radiolabeled HAL
101	91	Safety and clinical utility of different concentrations and instillation times
Total	**1,957**	

5.2 Review Strategy

After the not approvable letter for NDA (b) (4) was received, Photocure had discussions with the FDA, and a strategy for addressing the clinical comments of the not approvable letter was agreed upon. The following measures were implemented in the clinical study protocol for Study 305 to address the clinical comments in the not approvable letter issued to NDA (b) (4):

- Increased rigor and standardization in the pathology diagnosis were ensured by the design of the central pathology panel reads (central and local pathology read concurrence comparison)
- Documentation of the quality and thoroughness of the WL cystoscopy examination

The modified indication for NDA 22-555 is "Hexvix is as an adjunct to WL cystoscopy in the detection of non–muscle invasive papillary cancer of the bladder." Data in support of this detection indication in the present NDA are obtained primarily from a controlled, randomized, open label Phase 3, multicenter Study 305 in patients with papillary bladder cancer and a supportive recurrence reduction randomized, Phase 3, two-center Study 304 in patients suspected of having non–muscle invasive bladder cancer. The sponsor suggested that additional supportive efficacy data were provided from Studies 301, 302, and 303, which are studies submitted in support of the CIS indication in NDA (b) (4). Whereas during the review of NDA (b) (4) inconsistencies were revealed in the pathologic readings, the overall clinical data did not provide verifiable evidence of efficacy. Therefore, the efficacy results based on these earlier studies were not re-reviewed.

(b) (4)

Therefore, Study 305 becomes the single registration trial in support of this detection indication. Detection was evaluated from among 382 patients who received instillation of Hexvix solution into the bladder prior to WL and then BL cystoscopic mapping of suspicious bladder lesions. One or more pathologically valid lesions were found in 365 patients and 286 patients had one or more Ta or T1 bladder tumors. From among these, 47 patients had one or more Ta or T1 tumors detected by BL, but not by WL cystoscopy. These data are the basis for the detection efficacy claim.

Whereas this is a combination product, it requires separately provided approval by both CDER (Hexvix) and CDRH (Blue light PDD cystoscope) with mutually conforming (cross) labeling (21 CFR 3.2(e)(4).

5.3 Discussion of Individual Studies/Clinical Trials

Trial 305/04 –Detection and Recurrence Reduction Trial

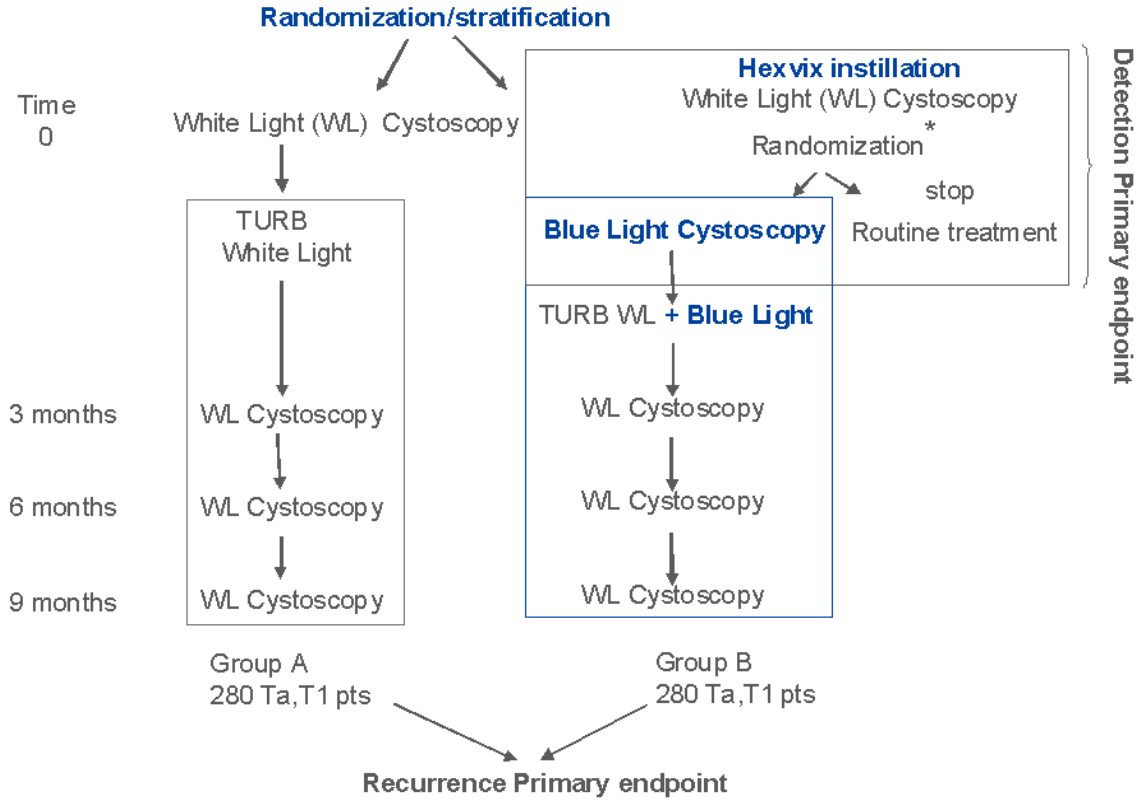
Trial 305 is the registration clinical trial in this NDA. Study 305 was a controlled, prospective, randomized multicenter Phase 3 trial investigating the safety and efficacy of Hexvix in detection of non-muscle invasive papillary bladder cancer and also reduction of early recurrence. The primary objectives of 305 were (1) to compare Hexvix cystoscopy with WL cystoscopy in the detection of histologically confirmed papillary bladder cancer in patients with papillary bladder cancer and (2) to compare early recurrence rate after Hexvix plus BL transurethral resection of the bladder (TURB) with WL TURB of the bladder alone in patients with non-muscle invasive papillary bladder cancer.

Trial 305 was initiated in January 2005 under IND 51224 and completed in September 2007. It was subject to a special protocol assessment, and the statistical analysis plan was discussed with the FDA (15 February 2007 meeting). As agreed with the FDA, a central pathology panel read was implemented to reduce variability and to ensure rigor of the pathology diagnosis. The central pathology panel consensus read was used as the standard of truth (SOT) for the detection primary endpoint as well as the detection secondary endpoints. For the recurrence primary endpoint, local pathology reads were utilized for both the baseline and recurrence tumor pathology. (b) (4)

The study design for Study 305 is diagrammed in **Figure 2.** Patients were initially randomized to either standard white light cystoscopy (Group A) or Hexvix instillation

(Group B). Patients initially randomized to the white light cystoscopy arm would serve as the white light arm for comparison to the Hexvix plus blue light arm for the "recurrence reduction" study. All patients that entered the Hexvix bladder instillation group participated in the initial detection arm of the study (right side of upper Figure). Following Hexvix instillation, all patients in this arm underwent standard white light cystoscopy. However, before proceeding with blue light cystoscopy, patients were re-randomized either to stop participation in the trial (not continue with blue light cystoscopy) or continue with blue light cystoscopy. A separate sealed envelope was opened in which instruction was given whether the Investigator should continue with a blue light inspection, mapping of all suspicious lesions seen under blue light and TURB (in the same cystoscopic examination) or to stop the procedure and give the patient standard treatment.

Figure 2: Study Design Trial 305



The mapping of lesions and suspicious areas was documented by video and on the CRF. The investigator documented the details of each lesion as follows: presence of lesion, type (papillary or flat), number of lesions and location (bladder neck anterior, trigone, ureteric orifice right, ureteric orifice left, posterior floor, right lateral wall, cranial

wall, left lateral wall, dome, anterior bladder wall and bladder neck posterior). For patients randomized to the Hexvix group and re-randomized to blue light, after white light inspection and documentation of all suspicious lesions seen under white light, the blue light was switched on and the location of all suspicious areas seen under blue light was documented on the CRF and by video.

Only after completion of mapping of lesions with both WL and BL cystoscopies, could the operator proceed with biopsying/resecting lesions mapped during the prior visualization cystoscopies. Biopsies could then be performed during illumination by standard white and blue light. All papillary lesions were resected and collected for histology at the same cystoscopic examination. The investigator documented the details of each lesion as follows: presence of lesion, type (papillary or flat), number of lesions and location (bladder neck anterior, trigone, ureteric orifice right, ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall and bladder neck posterior).

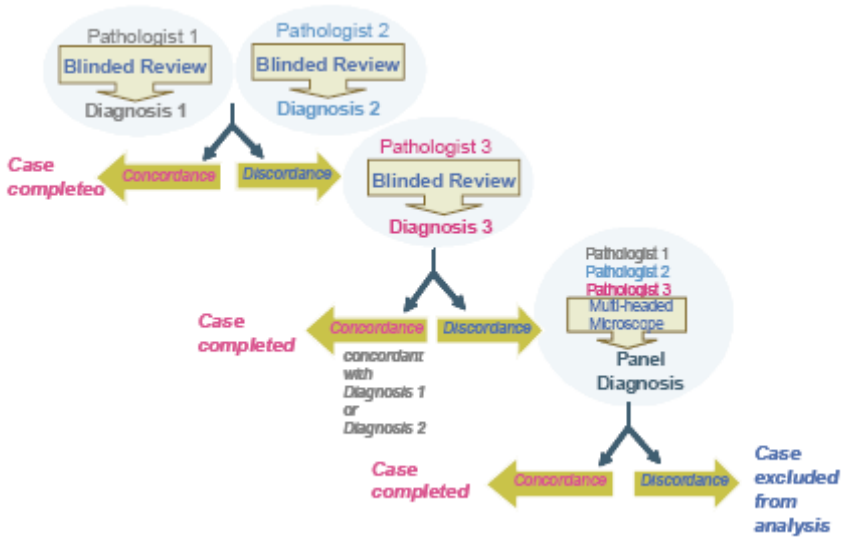
The reason for blinding the operator from knowing whether each white light examination would be followed by a blue light examination was to ensure thorough white light examinations, thus limiting bias. Thus, all subjects who received Hexvix instillation and had cystoscopic examinations and biopsies under both light sources participated in both the detection and recurrence segments of this trial. The detection primary endpoint was determined by a central panel pathology read process.

All biopsies and resected tissue of lesions and suspected areas were evaluated for histology both by a local pathologist and by a central pathology panel read for staging and grading. After mapping and taking biopsies of the lesions, the patient was treated according to standard practice at the hospital, at the discretion of the Investigator. The Investigator recorded in the CRF the patient treatment, based on the guidelines described in the protocol.

Subsequently, the same subjects who received Hexvix instillation and had cystoscopic examinations and biopsies/resections under both light sources (Group B) and the white light only without Hexvix (Group A) participated in the “recurrence” phase of this trial. Participation consisted of follow-up white light cystoscopy and biopsy of lesions observed at 3, 6 and 9 months (according to standard practice for recurrence in the United States). For the “recurrence” primary endpoint, initial and follow-up bladder cancers were determined by local pathology reads. The local pathology read was the SOT used to determine eligibility of patients to follow for “recurrence” and to confirm “recurrence”. Patients who were found to have invasive disease (stage T2 or higher) or who had no tumors were not eligible to continue in the study for analysis of the “recurrence” primary endpoint. Dysplasias were not classified as tumor “recurrence” since these lesions are not considered as malignant.

As discussed with and agreed to by the FDA, the central pathology panel read was implemented to reduce variability and to ensure rigor of the pathology diagnosis. The central pathology panel consensus read was utilized as the standard of truth (SOT) for the detection primary endpoint as well as the detection secondary endpoints. The procedure for the central pathology panel read is described in **Figure 3**. Initially two independent pathologists perform blinded review reads. If there is agreement in the diagnosis by both, the case is completed. If there is discordance, a third independent pathologist performs a blinded review read. If the diagnosis by reader #3 is concordant with diagnosis #1 or #2, that read becomes the SOT read. If discordance still exists after three independent reads, a panel pathology read will be performed by three pathologists utilizing a multi-headed microscope to determine a panel diagnosis. This panel diagnosis, if determined becomes the final read, if concordance can not be reached the case is excluded from the analysis. 1

Figure 3 : Flow Chart of Central Pathology Panel Read Trial 305



Trial 305 Population (ITT)

Inclusion Criteria

- Either sex aged ≥ 18 years
- > One following criteria confirmed on outpatient cystoscopy
    - > one bladder tumor

1 The concordance criteria for the central pathology panel read were specified in the document "Central Pathology Read Procedure," which was submitted to the FDA on 03 December 2007 (SN081).

- Recurrence < 12 months
- > one papillary lesion at time of recurrence

Exclusion Criteria

- Gross hematuria
- Porphyria
- Known allergy to hexyl 5-aminolevulinate HCl or a similar compound
- Pregnant or breast-feeding women
- Patients who have received BCG or chemotherapy within 3 months prior to Hexvix instillation, except for a single dose of chemotherapy for prevention of seeding after resection

Trial 305 – Co-primary efficacy endpoints

1) Initial Detection Primary Endpoint:

The proportion of patients in the Hexvix group with histologically-confirmed tumors (Ta or T1) that had at least one such tumor found in blue light cystoscopy but not in white light cystoscopy. This was defined as the number of patients with at least one histologically confirmed lesion of type Ta or T1 through the Standard of Truth central pathology panel read, that was detected in blue light but not in white light divided by the number of patients with at least one confirmed lesion of type Ta or T1.

2) Follow-up Detection Primary Endpoint:

Comparison of the proportions of patients in the white light cystoscopy and Hexvix groups who underwent TURB for a histologically-confirmed (local pathologist) Ta or T1 tumor who had a recurrence, defined as any type of histologically-confirmed (local pathologist) tumor (either a CIS, Ta, T1 or T2-T4 tumor) found at either 3, 6 or 9 months.

Initial Detection and Follow-up Detection Analyses Criteria

Different criteria were used for defining the analysis sets for the detection endpoints (primary and secondary) and for the ("recurrence") primary endpoint in Trial 305, such that the intent-to-treat (ITT) and per protocol (PP) analytic sets for the "recurrence" primary endpoint (recurrence ITT and PP analytic sets) are slightly different from the ITT and PP analysis sets for the detection endpoints (detection ITT and PP analysis sets). This is because local pathology was used to define the patients with Ta or T1 for the follow-up detection ("recurrence") primary endpoint, whereas central pathology was used to define the patients with Ta or T1 for the initial detection primary endpoint. In addition, the ITT and PP populations for the detection endpoints included patients with no tumors, patients with only CIS tumors and patients with muscle invasive tumors (T2 and higher stage). The analytical population for the follow-up detection endpoint was limited to patients who had a Ta or T1 lesion (local pathology) detection during the initial cystoscopy.

Study 305 Efficacy Results:

Analyses were performed for the co-primary endpoints of initial detection and follow-up detection (”recurrence”). The initial detection endpoint efficacy analysis was confined to data from the “Hexvix group”, i.e., patients randomized to Hexvix cystoscopy who continued with the blue-light procedure. The follow-up (“recurrence”) endpoint efficacy analysis used data from the two randomized groups (“white light” group compared to “Hexvix group”).

Trial 304 – Supportive Follow-up Detection Trial

Trial 304 was an open-label, comparative, randomized, Phase 3, two-center trial in patients suspected of having non–muscle invasive bladder cancer and is considered the supportive study in this NDA. The primary objective of Study 304 was to compare tumor recurrence rates after WL and fluorescence-guided BL TURB versus standard WL TURB alone in patients with macroscopically (papillary) noninvasive bladder tumors.

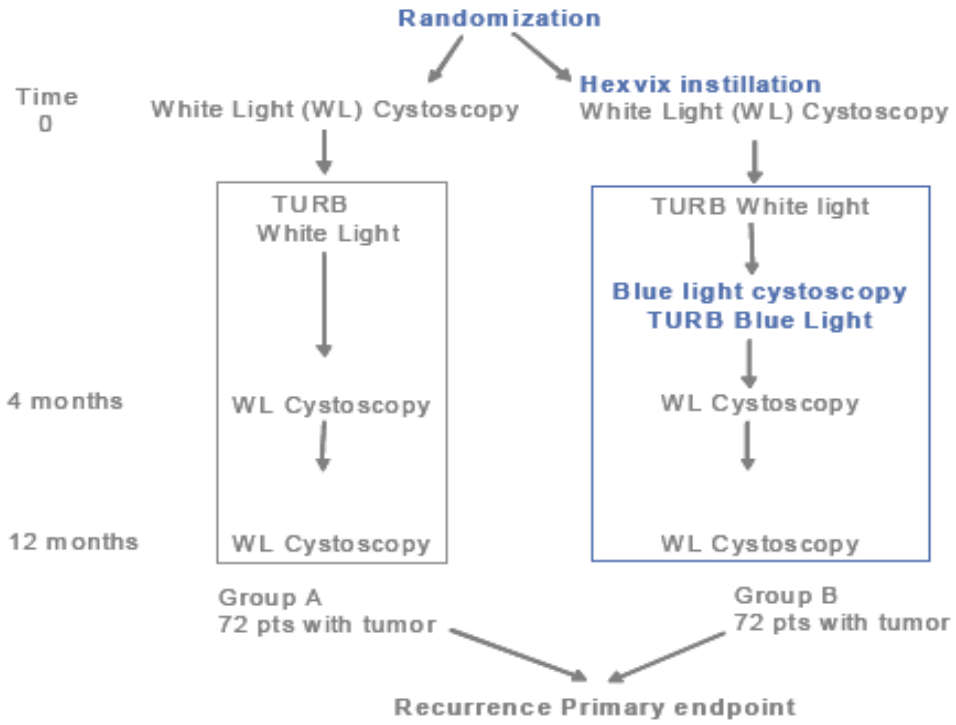
Trial 304 - Primary efficacy endpoint

“Recurrence” Primary Endpoint: Comparison of the proportions of patients with histologically confirmed recurrence at 4 months and one year following white light cystoscopy with TURB and blue light cystoscopy with TURB.

Trial 304 was an open-label, comparative, randomized, Phase 3, two-center trial in patients suspected of having non–muscle invasive bladder cancer and is considered the supportive study in this NDA. The primary objective of Study 304 was to compare tumor recurrence rates after 12 months following WL and fluorescence-guided BL TURB versus standard WL TURB alone in patients with macroscopically (papillary) noninvasive bladder tumors.

In study 304, patients were randomized in a 1:1 ratio to either Hexvix or white light (**Figure 4**). Patients underwent biopsy and/or resection of bladder tumors at the initial white light examination. For patients with only CIS, or Ta or T1 lesions, follow-up cystoscopy was performed at months 4, 8 and 12. Site pathology reads were used for the baseline assessment for inclusion and the outcome assessments for efficacy. The primary endpoint was a comparison of the proportion of patients with ‘follow-up detection recurrence” between the study groups.

Figure 4 : Study Design Trial 304



Comparison of Two Trials

These two trials are quite similar in design; both were randomized, prospective, comparative, controlled, Phase 3 trials in patients with non-muscle invasive bladder cancer, and both trials utilized the Karl Storz PDD system with D-light C as the light source. However, some important design elements are different; the main differences in design are the number of centers, the pathology read procedures, the follow-up times, bias reducing measures and the size and characteristics of the patient populations. A comparison of the main trial design features of Studies 305 and 304 are shown in **Table 2.**

Table 2 : Comparison Eligibility, Objectives Endpoints Design, Bias Reduction Pathology Reads and Follow-up in Trials 305 and 304

	305 Trial	**304 Supportive Trial**
Patient Eligibility	Multiple new bladder tumors or Recurrence >1 papillary lesion or Recurrence bladder cancer < 12M	Suspected bladder cancer before enrollment (Based on out-patient cystoscopy)
Primary Objective(s)	**Detection** Compare Hexvix +BL cystoscopy with WL cystoscopy in detection of histologically-confirmed papillary bladder cancer **Follow-up Detection** Compare early "recurrence" rate (<9M) after Hexvix+BL TURB with WL TURB in patients with papillary bladder cancer	**Follow-up Detection** Compare "recurrence" rate (< 12M) after Hexvix+BL TURB with WL TURB in patients with superficial bladder cancer (CIS, Ta, T1) (Ta, T1)
Primary Endpoint(s)	**Detection** Proportion subjects with ≥ 1 histologically-confirmed papillary bladder cancer (Ta or T1) detected with Hexvix BL and not by WL cystoscopy **Follow-up Detection** Comparison proportions of Hexvix + BL to WL cystoscopy TURB patients (Ta or T1 tumor) with histologically-confirmed "recurrence" at 3, 6, or 9 M	**Follow-up Detection** Comparison proportions of Hexvix+ BL to WL cystoscopy TURB patients with "recurrence" at 4M and 12 M
Design	RC Phase 3 prospective, comparative Hexvix +BL cystoscopy with WL cystoscopy and TURB	RC Phase 3 prospective, comparative Hexvix +BL cystoscopy with WL cystoscopy and TURB
Bias Reduction Design	To ensure thorough WL mapping Re-randomization post WL cysto 1 - Continue to BL cystoscopy (detection and 'recurrence" segments) 2 - Exit from study	To ensure thorough WL mapping all lesions biopsied or resected post WL cysto before BL cysto
Pathology Read	**Central** – baseline and primary and secondary detection endpoints **Local** –baseline and "recurrence" endpoints	**Local** – all endpoints
WL cysto Follow-up	3, 6, 9 months for "recurrence"	4 & 12 months for "recurrence"

Both trials assessed tumor recurrence as a primary endpoint, but the duration of follow-up in each study was different; 9 months in 305 and 12 months in 304. Furthermore, 305 had an additional primary endpoint of tumor detection. Another difference between the two trials is that the sample size in 304 is approximately 25% that of 305. 305 also had an additional design element to reduce bias as compared to 304. In 305, patients dosed with Hexvix were re-randomized to continue or not to continue with Hexvix cystoscopy after WL cystoscopy. It should also be noted that in 304, after completion of mapping with WL cystoscopy, all lesions were biopsied and resected before blue-light cystoscopy. Thus, none of the lesions detected with blue light had been detected during WL cystoscopy.

Trial 103 – Pharmacokinetic Trial

A Phase 1, radiolabeled pharmacokinetic trial was conducted to evaluate the systemic absorption of Hexvix following intravesical administration and to assess pharmacokinetics following intravenous administration in eight subjects.

Trial 201 - Phase 2 Dose-Confirmatory Trial

Trial 201 was a multicenter, within-patient controlled, comparative Phase 2 trial in 52 patients with a suspicion of bladder cancer. The trial was designed to evaluate the diagnostic value and the safety profile of Hexvix cystoscopy and was conducted to confirm the choice of dosing regimen selected in Trial 001. The trial utilized a within-patient, controlled comparison of Hexvix and white light cystoscopy. Hexvix 8 mM solution (50 mL) was instilled for 1 hour. After white light mapping followed by blue light mapping a total of five selected biopsies were taken from normal-appearing urothelium under white light for establishment of standard-of-truth. Thereafter, biopsies were taken from all visible lesions detected under white light and from all additional fluorescing lesions and suspicious areas under blue light, consecutively, with a maximum of four fluorescing flat lesions per patient.

Trial 301 – Phase 3 Comparative Trial

Study 301 was a multicenter, open label, within-patient controlled, comparative, Phase 3 study in 286 patients with suspected or verified bladder cancer. The study was designed to compare Hexvix with white light cystoscopy in identifying patients with additional CIS lesions with Hexvix compared with white light cystoscopy. Hexvix 8 mM solution (50 mL) was instilled for 1 hour. After white and blue light mapping, biopsies were taken from all visible, non-fluorescing lesions and suspicious areas under white light and from all additional fluorescing areas under blue light. In addition, one random biopsy from normal-appearing, non-fluorescing urothelium was taken as a reference of normal tissue for the pathologist.

Trial 302 - **Phase 3 Comparative Trial**

Study 302 was a multicenter, within-patient controlled, comparative Phase 3 trial in 311 patients with suspected or verified bladder cancer. The study was designed to compare Hexvix with white light cystoscopy in identifying more patients with CIS detected than with white light cystoscopy only. Hexvix 8 mM solution (50 mL) was instilled for 1 hour. After white and blue light mapping, biopsies were taken from all visible, non-fluorescing flat lesions and suspicious areas under white light and from all additional fluorescing flat lesions under blue light. All papillary lesions observed were resected according to hospital routines. In addition, one random biopsy from normal-appearing, non-fluorescing urothelium was obtained to provide a normal biopsy for pathological reference.

Both Trials 301 and 302 had within-patient comparisons of white light cystoscopy with Hexvix (blue light fluorescence) cystoscopy to evaluate the efficacy of Hexvix cystoscopy for the detection of CIS. Patient populations in both trials were similar. However, the endpoints were different in each trial. The primary endpoint in Trial 301 was the proportion of patients who had more CIS lesions found by Hexvix cystoscopy than were found with white light cystoscopy. The primary endpoint in Trial 302 was the number of patients with CIS lesions detected by Hexvix cystoscopy but not by white light cystoscopy. Thus, Trial 301 evaluated the primary efficacy of Hexvix cystoscopy in patients on a biopsy level while Trial 302 evaluated the efficacy of Hexvix cystoscopy on a patient level. The sponsor performed a post hoc analysis to determine the number of patients with CIS lesions detected by Hexvix cystoscopy but not by white light cystoscopy in study 301. The sponsor then considered that these two studies should be combined to support the efficacy claim for Hexvix. However, in pre-NDA discussions, the FDA notified the sponsor that only Study 302, that evaluated efficacy of Hexvix cystoscopy on a patient level, would be considered as supporting an efficacy claim.

Trial 303 – Phase 3 Study that Compared Intended Patient Management Based on Cystoscopic Findings

Trial 303 was a multicenter, within-patient controlled, comparative, Phase 3 trial in 162 patients with suspected or verified bladder cancer. The primary objective of the trial was to compare the intended management of patients with bladder cancer following diagnosis with Hexvix cystoscopy as compared with the management based upon white light cystoscopy only.

Hexvix 8 mM solution (50 mL) was instilled into the bladder for 1 hour. After white light mapping, the investigator opened a sealed envelope for each patient to determine if the patient was to continue with blue light cystoscopy or not. Patients who continued with Hexvix cystoscopy underwent blue light mapping after which biopsies were taken from all visible, non-fluorescing lesions and suspicious areas under white light and from all additional fluorescing areas under blue light. In addition, one random biopsy from normal-appearing, non-fluorescing urothelium was obtained as a sample of normal

mucosa for the pathologist. All biopsies were provided to a local and a central pathologist who were both blinded to the lesion identification method. The pathology results from the central pathologist were collated into two sets of results for each patient (results from Hexvix cystoscopy and results from white light cystoscopy) and provided in a randomized fashion to an independent urologist, along with medical history and the findings of the respective cystoscopic examination.

The randomization procedure was applied to ensure that the independent urologist did not assess the two sets from the same patient after each other. The independent urologist then provided a recommended patient treatment plan for each of the two sets per patient, based on the European (EAU) guidelines on bladder cancer. The results of the local pathologist were evaluated by the local urologist (investigator) and served as the basis for the actual treatment of the patient. The results from the central pathologist and the independent urologist were used for the efficacy analyses to compare whether blue light cystoscopy added valuable management information.

Current Gold Standard of Diagnosing Bladder Cancer

The current gold standard of diagnosing bladder cancer is a combination of visual inspection of the bladder with an endoscope and white light illumination (WL cystoscopy) and biopsies for histological verification. White-light cystoscopy is used conventionally to detect lesions in the bladder for patients with known or suspected bladder cancer. TURB removes the tumor and allows for pathologic analysis of the resected or biopsied specimen, establishing the diagnosis and providing important information about the tumor grade and depth of bladder invasion. However, tumors such as flat carcinomas (particularly CIS), dysplasia, multifocal growth and microscopic lesions are often overlooked by conventional WL cystoscopy.

Pathological Examination of Biopsy Specimens

In Studies 305 and 304 the pathologists were blinded as to whether the samples were taken from a normal-appearing area, a suspicious non-fluorescing area, or a fluorescing area during evaluation. For Study 305, a central pathology panel read was implemented to reduce variability and to ensure rigor of the pathology diagnosis. The central pathology panel consensus read was utilized as the standard of truth (SOT) for the detection primary endpoint as well as the detection secondary endpoints. For the recurrence primary endpoint, local pathology reads were utilized for both the baseline and follow-up tumor pathology specimens. For Study 304, local pathology reads were utilized for both the baseline and follow-up tumor pathology specimens.

Lesions were staged according to the International Union Against Cancer (UICC)/ American Joint Committee on Cancer (AJCC) 1997 system. Flat lesions were graded according to the World Heath Organization (WHO)/International Society of Urological Pathology (ISUP) 1998 consensus classification of urothelial (transitional cell)

neoplasms of the urinary bladder and papillary lesions were graded according to WHO 1973.

6 Review of Efficacy

Efficacy Summary

In Study 305, 286 patients had at least one confirmed Ta or T1 lesion by central pathology read, and 47 (16%) patients had at least one Ta or T1 lesion seen in blue light that was not seen in WL; this result was statistically significant ($p < 0.001$; 99% CI: 11% to 23%). Therefore, the proportion of patients where at least one additional Ta/T1 tumor was seen with Hexvix Group BL and not with WL was larger than 10%, the success criteria agreed to with the FDA. Statistical significance was not demonstrated for reduction in early follow-up detection in either Study 305 or Study 304.

6.1 Indication

> "Hexvix Solution is a diagnostic imaging agent indicated for photodynamic blue light cystoscopy performed with Karl Storz Photodynamic Diagnosis (PDD) system, as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary cancer of the bladder in patients with known or suspected bladder cancer"

6.1.1 Methods

The integrated analysis of efficacy (IAE) provided in this NDA focused on the data from registration Study 305 and supportive Study 304. Efficacy data from registration Study 305 are presented in support of the detection indication, while data from Study 305 and Study 304 are presented separately as supportive data (b) (4) . Data from Studies 301, 302, and 303 that focused on the detection of papillary tumors in patients with bladder cancer were not integrated with Study 305 data. Data from Trials 305, 303, 303, 302, 301 and 201 contributed to the 1,324 patients who received Hexvix and were included in the Safety Data Set.

Hexvix is used in combination with the Karl Storz PDD system. The light source of the PDD system used in the studies presented in the original NDA (301, 302 and 303) was the 'D-Light'. Due to technical development and evolution in the field of PDD systems, the light source has been updated to 'D-Light C with a higher energy level. All other components of the Karl Storz PDD system are unchanged. The Registration clinical trial 305 and the supportive clinical trial 304 have both been performed with the latest and most current version of the light source (D-Light C). The safety and efficacy data from

the clinical studies show no apparent change in the efficacy or safety profile of the Karl Storz PDD system using the updated light source compared to the earlier version of the light source. However, CDRH is concurrently conducting an evaluation of the safety of the updated blue light system.

6.1.2 Demographics

In Study 305, the majority of intent-to-treat (ITT) patients in the two study groups (Hexvix, WL) were aged 65 years or older (Hexvix: 67%; WL: 68%), and were male (Hexvix: 76%; WL: 79%). Almost all patients were white (Hexvix: 92%; WL: 96%). In Study 304, information about ethnic group, height, and weight was not collected; however, the two study groups were quite comparable with respect to age and sex, with most patients being male and aged 65 years or more. For the most part, the patient demographics in the other supportive studies were comparable to those in Studies 305 and 304 and similar to the general population affected by bladder cancer, which is the population expected to receive Hexvix cystoscopy after approval.

For Studies 305 and 304, different criteria were used for defining the analysis sets for the detection endpoints (primary and secondary) and for the "recurrence" primary endpoint. In this regard, the ITT and per protocol (PP) analysis sets for the detection endpoints are slightly different from the ITT and per protocol (PP) analysis sets for the recurrence primary endpoints. This difference is because central pathology was used to define the patients with Ta or T1 tumors for the detection primary endpoint in Study 305, whereas local pathology was used to define the patients with Ta or T1 tumors for the recurrence primary endpoint for both studies (305, 304). In addition, for both studies, the ITT and PP populations for the detection endpoints included patients with no tumors, patients with only CIS tumors and patients with muscle invasive tumors (Stage T2 and higher); whereas only patients with Ta or T1 confirmed by the local pathologist were included in the recurrence primary endpoint.

6.1.3 Subject Disposition and Baseline Characteristics

Summaries of the patient baseline characteristics and disposition in Studies 305 and 304 follow. Registration Trial 305 was divided into two segments, the initial detection segment and the early (9 months) follow-up detection segment. Study 304 was smaller and was designed to evaluate early (12 months) follow-up detection (referred to as "recurrence" by the Sponsor).

Trial 305

A total of 814 patients gave informed consent and were included in the study at 28 centers in the USA, Canada and Europe (US 17, Canada 2, Europe 9). There were 35

training patients, i.e. the first 5 patients recruited at centers with no previous experience of using Hexvix who were given Hexvix and had cystoscopy under blue and white light but were assessed for safety only. Of the 779 patients randomized, 395 (51%) patients were randomized to the Hexvix group and 384 (49%) to the white light group. Only those patients randomized to the Hexvix Group were included in the detection segment of the trial (**Table 3**).

The number of patients recruited at each center ranged between 1 (Centers 4, 305 and 401) and 92 (Center 304). Almost 80% of the patients (647 patients) were enrolled by half (14) of the centers. Thirteen (11%) of the discontinued patients were re-randomized not to continue after the initial procedure. These are the patients who had Hexvix instilled into the bladder and underwent only white light cystoscopy. The patients in the Hexvix group were then re-randomized and these 13 patients were allocated not to continue with blue light cystoscopy. The re-randomization process was included to minimize the potential for bias during inspection under white light. These patients were not followed up for detection or recurrence, only for safety, as planned in the protocol.

Table 3 : Patient Disposition – Initial Detection Segment Study 305

Patients	**N = 814** 28 Centers	
	Hexvix Group Detection segment	**WL Group**
Number of patients included	N = 430	N = 384
Training patients excluded	35	-
Randomized to Hexvix instillation	395	-
Re-randomized out of Blue Light exam	13	-
Number of patients cysto exam WL & BL	382	-
Patients with ≥ 1 valid pathology result	**365**	**361**

Patients who did not have histologically confirmed Ta or T1 tumors were deemed to have completed the study after the cystoscopy procedure and safety follow-up. Of the 395 patients who were initially randomized to the Hexvix group, 116 (29%) patients were not eligible to continue in the study for the recurrence endpoint. Of the 384 patients who were initially randomized to the white light group, 101 (26%) patients were not eligible to continue in the study for the recurrence endpoint. Only patients with histologically confirmed Ta or T1 tumors (local pathology read) at baseline were eligible for the follow-up detection Primary Endpoint. Training and re-randomization was not applicable in this arm of the study and so all of these were planned discontinuations of

patients who were found not to be eligible for the Recurrence Primary Endpoint once the histology data were available.

Therefore, 279 (71%) of the 395 patients randomized to the Hexvix group and 283 (74%) of the 384 patients randomized to the white light group had the potential to be followed in the study for the "Recurrence" Primary Endpoint. However, an additional 8 patients in the Hexvix group and 3 patients in the white light group had procedural reasons for not continuing. Therefore, 271 patients in the Hexvix group and 280 patients in the white light group were eligible to continue in the study for up to 9 months. Patient disposition did not accurately reflect the correct reasons for patients stopping the study. Patient disposition was determined from the analysis sets and from relevant individual patient data.

A total of 551 patients in the ITT Set had histologically-confirmed Ta or T1 tumors (local pathology read) at baseline and were eligible for the analysis of the "Recurrence" Primary Endpoint (Table 4). Of these, 271 (49%) patients were in the Hexvix group and 280 (51%) patients were in the white light group. In the Hexvix group, 88 (33%) patients stopped the study because they reached the endpoint for "recurrence". A further 44 (16%) patients discontinued the study without reaching an endpoint. Similarly, in the white light group, 107 (38%) patients stopped the study because they reached the endpoint for follow-up detection and a further 49 (18%) patients discontinued the study without reaching an endpoint.

Table 4 : Patient Disposition – Follow-up Detection Segment 305

Patients	Hexvix Group		WL Group		Total	
Number of Patients	n	%	n	%	n	%
All patients included	430		384		814	
Training patient	35		Not applicable		35	
Randomized	395	100	384	100	779	100
Planned discontinuation from study	116	29	101	26	217	27
Re-randomized out of BL group	13	11	Not applicable		13	6
Tumor type not eligible to follow	103	89	101	100	204	94
Planned to continue in study	279	71	283	74	562	72
Unplanned discontinuation *	8	3	3	1	11	2
Eligible for "recurrence" analysis	271	97	280	99	551	98

* = Not treated, no cystoscopy or no BL inspection

Major baseline characteristics for the randomized study group ITT population are shown in **Table 5**. These characteristics are largely the same in the initially randomized population as well as the population undergoing the follow-up detection assessment. The average age in both groups was approximately 70 and over three quarters of the patients were men. Over 90% of the patients were white and most (approximately 60%) had a history of prior papillary bladder cancer. Twenty to twenty-five percent of the patients had previously received BCG and at enrollment approximately 10% related a history of hematuria. Baseline characteristics were similar among the patients undergoing the follow-up detection endpoint assessment.

Table 5 : Study 305 Baseline Characteristics

Group	Hexvix n = 365	WL n = 361
Age (mean, yrs)	69	70
Male (%)	76%	79%
White (%)	92%	96%
Recurrent tumor (%)	59%	58%
Prior BCG	20%	25%
Hematuria	11%	9%

Trial 304

In Trial 304, patients who did not have histologically confirmed Ta, T1 or CIS tumors detected on cystoscopy were deemed to have completed the study post cystoscopy. and were not included in the supportive data. A total of 68 (29%) patients did not have histologically confirmed Ta, T1 or CIS tumors detected on cystoscopy and were not eligible to be followed for the recurrence analysis. Of the 233 patients included, 115 (49%) were randomized to the Hexvix cystoscopy group and 118 (51%) to the white light cystoscopy group. One hundred and seventy-five (75%) patients were included at Centre 1 and 58 (25%) patients were included at Centre 2. The planned number of patients to be included in the study was 164. However more patients were enrolled to allow for the patients who would not be eligible to continue in the study for evaluation of recurrence. One hundred and sixty-five (71%) patients were found to have histologically confirmed Ta, T1 or CIS tumors after cystoscopy and were eligible for the recurrence analysis. Fifty-five (24%) patients discontinued the study at Month 4 and 110 (47%) patients continued in the study to Month 8 or 12. Forty-one (36%) patients in the Hexvix cystoscopy group and 41 (35%) patients in the white light cystoscopy group continued in the study for 8 or 12 months without recurrence. A summary of patient disposition is provided in **Table 6**. Study 304 was performed in only two centers located in Denmark.

Table 6 : Patient Disposition - Supportive Trial 304 (ITT)

Data Set	Hexvix Group		White Light G		Total	
	n	%	n	%	n	%
All patients randomized	115		118		233	
Excluded from recurrence	36	31	32	27	68	29
Planned inclusion for "recurrence"	79	69	86	73	165	71
Last visit Month 4	23	20	32	27	55	24
"Recurrence" at Month 4	14	12	26	22	40	17
No follow-up visits	5	4	0	0	5	2
Imputed "recurrence" Month 4	1	1	3	3	4	2
Imputed "recurrence Month 12	3	3	3	3	6	3
Last visit Month 8 or 12	56	49	54	46	110	47
No "recurrence"	41	36	41	35	82	35
"Recurrence" at Month 4	0	0	1	10	1	<1
"Recurrence" at Month 12	12	10	12	10	24	10
Imputed "recurrence Month 12	3	3	0	0	3	1

6.1.4 Analysis of Primary Endpoint(s)

The primary detection endpoint efficacy analysis in support of this NDA was conducted on the data from Trial 305 derived from patients randomized to Hexvix cystoscopy who continued with the blue-light procedure. The "recurrence" primary endpoint data were derived from patients in both Trial 305 and 304 with follow up cystoscopic examinations for 9 months (305) and 12 months (304). Analyses were performed for both detection and follow-up detection ("recurrence") and the results follow.

Detection Primary Endpoint Analysis

The detection primary endpoint is the proportion of patients with one or more Ta or T1 tumors detected by Hexvix cystoscopy only. The proportion of patients with one or more Ta or T1 tumors found by Hexvix only is defined as the number of patients with at least one histologically-confirmed Ta or T1 lesion (according to the SOT central panel read for Study 305) that was detected with Hexvix cystoscopy but not with WL cystoscopy divided by the number of patients in the Hexvix cystoscopy group with at least one confirmed Ta or T1 lesion. This endpoint was based on results from the SOT central panel read.

Results for the detection primary endpoint analysis for the ITT population are presented in **Table 7.** In Study 305, 286 patients had at least one confirmed Ta or T1 lesion by

central pathology read, and 47 (16%) patients had at least one Ta or T1 lesion seen in blue light that was not seen in WL; this result was statistically significant ($p < 0.001$; 99% CI: 11% to 23%). Therefore, the proportion of patients where at least one additional Ta/T1 tumor was seen with Hexvix Group BL (Group B) and not with WL (Group A) was larger than 10%, the success criteria agreed to with the FDA as part of the Special Protocol Assessment process.

Table 7 : Analysis of the Initial Detection Primary Endpoint Trial 305 (ITT)

Patients with any pathology Hexvix Group n = 365	**Hexvix Group n (%)**
With Ta or T1 detected by WL and/or BL	**286/365 (78%)**
With Ta or T1 detected only by BL	**47/286 (16%)**
P-value	**0.001**

Results for the detection primary endpoint analysis for the PP population are presented in **Table 8**. Results for the PP population were similar to those for the ITT population.

Table 8 : Analysis of the Detection Primary Endpoint Trial 305 (PPS)

Patients	**Central Pathology** Hexvix Group N = 352 n (%)
With ≥ 1 valid pathology result	**352 (100 %)**
With ≥ 1 confirmed Ta or T1 tumor	**278 (79 %)**
With ≥ 1 Ta or T1 tumor with BL but not WL	**47 (17 %)**
p-value	**0.0005**

In addition, per the FDA's request, the primary detection endpoint analyses were repeated for Study 305 by comparing the results from the local pathology with those of the central pathology. These results are presented in **Table 9**. In this study, comparison reveals that both local and central pathology reads were similar. A total of 44 (15.8%) patients had at least one Ta or T1 lesion seen in blue light that was not seen in WL when the local pathology data were used, compared to 47 (16.9%) patients when the central panel read was used. The concordance between results when using the central and local pathology reads in Study 305 demonstrates the consistency of the data.

An analysis was performed to determine how many patients had local and central pathology results that agreed or disagreed. It was found that 11 patients had at least one Ta or T1 lesion seen according to the central panel read, but not according to the local pathology data. Conversely, there were 8 patients that had at least one Ta or T1 lesion seen according to the local pathology results, but not according to the central panel read.

Table 9 : Comparison of Analyses of the Detection Primary Endpoint by Central and Local Pathology Reads Trial 305 (ITT)

Patients	Central Pathology	Local Pathology
	Hexvix Group N = 352 n (%)	Hexvix Group N = 365 n (%)
With ≥ 1 valid pathology result	352 (100 %)	365 (100 %)
With ≥ 1 confirmed Ta or T1 tumor	278 (79 %)	279 (76%)
With ≥ 1 Ta or T1 tumor with BL but not WL	47 (17 %)	44 (16 %)

Trial 305 - Early Follow-up Detection "Recurrence" Primary Endpoint Analysis

The recurrence primary endpoint is the proportion of patients in each group who underwent TURB for a histologically-confirmed Ta or T1 tumor and who had a recurrence (defined as any type of histologically-confirmed tumor: CIS, Ta, T1, or T2-T4) found within the study follow-up period (9 months for Study 305 and 12 months for Study 304). These endpoints were based on results from the local pathologist reads. Results for the recurrence primary endpoint analysis ITT population are presented for Study 305 in **Table 10.** The number of patients with recurrence included imputed data for 57 patients in the Hexvix blue light group and 60 in the white light group.

Table 10 : Follow-up Detection ("Recurrence") Primary Endpoint Analysis Trial 305 (ITT)

Patients eligible for Follow-up Detection N = 551	Blue Light (N=271)	White Light (N=280)
Total number patients with follow-up detection ("recurrence")	128	157
Proportion Patients with Follow-up Detection "recurrence" (99%CI)	47 % (39-55)	56 % (48-64)
P value	0.03	

Results for the recurrence primary endpoint analyses ITT population Study 304 are presented in **Table 11** and **Table 12**. Table 11 displays the results utilizing the patients with Ta or T1 lesions at baseline (excludes patients with only CIS). Table 12 displays the results utilizing the patients with CIS, Ta or T1 lesions at baseline. Both trials show similar recurrence rates between groups at one year and statistically unsuccessful outcomes.

Table 11 : Follow-up Detection ("Recurrence") Primary Endpoint Analysis Trial 304 with Ta or T1 Lesions - (ITT)

Patients with Ta or T1 Local Pathology Read – Baseline		
Eligible for Follow-up Detection "Recurrence" N=160	Blue Light Group N = 77	White Light Group N = 83
Patients with Follow-up Detection "Recurrence"	12 Months	12 Months
	37(48%)	44 (53%)
P value	0.53	

Table 12 : Follow-up Detection ("Recurrence") Primary Endpoint Analysis Trial 304 with CIS, Ta or T1 Lesions - (ITT)

Patients with CIS, Ta or T1 Local Pathology Read – Baseline		
Eligible for Follow-up Detection "Recurrence" N=165	**Blue Light Group N = 79**	**White Light Group N = 86**
Patients with Follow-up Detection "Recurrence"	**12 Months**	**12 Months**
	38(48%)	**45 (53%)**
P value	**0.58**	

In Study 305, 143 (53%) patients in the Hexvix cystoscopy group completed the study through the 9-month follow-up visit without any recurrence, compared with 123 (44%) patients in the WL cystoscopy group. The remainder of the patients either had a recurrence or had an incomplete follow-up. At 3, 6, and 9 months in Study 305, the proportion of recurrences in the WL-cystoscopy group was greater than that in the Hexvix-cystoscopy group, with most recurrences in both study groups occurring at 3 months (**Table 13**). Incomplete cases (e.g., no 9 months follow up, lack of pathology data for a recurrence that was observed visually on the follow up cystoscopic examination) were imputed with the result recurrence equal to "Yes' in the ITT analysis, as a worst case scenario. The number of imputed cases was similar in the two study groups (56 for Hexvix cystoscopy group and 59 for WL cystoscopy group). Approximately 40% of "recurrence" cases were based on imputations. With these imputations, 47% of patients in the Hexvix cystoscopy group and 56% of patients in the WL cystoscopy group had a recurrence (a difference of 9%).

When using the Cochran-Mantel-Haenszel (CMH) chi-square test, the difference between the two proportions was statistically significant at the 5% level ($p = 0.0257$. However, it was not statistically significant at the 1% level, which is the significance level specified in the SAP. The relative reduction in recurrence for the Hexvix cystoscopy group compared with that for the WL cystoscopy group was 15.8% (99% CI: 4% to 32%).

Table 13 : Patients with Tumor "Recurrence" by Timepoint - 305 (ITT Subset)

	Patients with Ta or T1 Local Pathology Read					
n=551	**Blue Light Group n=271**			**White Light Group n=280**		
	3 M	**6M**	**9M**	**3 M**	**6M**	**9M**
	n=251	**n=190**	**n=164**	**n=246**	**n=185**	**n=142**
Discontinued	**20**	**17**	**1**	**34**	**6**	**9**
Recurrence	**80**	**34**	**14**	**100**	**33**	**24**
Confirmed	**44**	**17**	**11**	**55**	**28**	**15**
Imputed	**36**	**17**	**3**	**45**	**5**	**9**
No follow-up	**20**	**-**	**-**	**34**	**-**	**-**
Missing data	**13**	**14**	**3**	**7**	**4**	**9**
Missing visit	**3**	**3**	**-**	**4**	**-**	**-**
Visit >2 W early	**-**	**-**	**-**	**-**	**1**	**-**

For the most part, results from Study 304 trend similarly to those observed in Study 305. In the ITT analysis, 40 (52%) patients in the Hexvix cystoscopy group completed the study without any recurrence compared with 39 (47%) patients in the WL cystoscopy group. The remainder of the patients either had recurrence during the 12-month follow-up or had incomplete follow-up, and incomplete cases were imputed as in Study 305. Twice as many Hexvix BL Group patients were imputed as compared to the patients in the WL cystoscopy group. With these imputations, 37 (48%) patients in the Hexvix cystoscopy group and 44 (53%) of the patients in the WL cystoscopy group with Ta or T1 lesions at baseline had a recurrence The difference between the two proportions 7% (CMH chi-square test) was not statistically significant (p = 0.53). **Table 14** summarizes the patient population disposition based on patients with CIS, Ta and T1 lesions at baseline.

Table 14 : Recurrence Analysis Study 304 (ITT Set) & Patient Population Disposition

Patients with CIS, Ta, or T1 Local Pathology Read				
N=233	**Hexvix Group n=115**		**White Light Group n=118**	
Eligible for Recurrence	**N = 79**		**N = 86**	
	4 M	**8 &12 M**	**4 M**	**8 &12 M**
Last Visit	**23**	**56**	**32**	**54**
Recurrence	**n=20**	**n=18**	**n=30**	**n=15**
	38 (48%)		45 (52%)	
Recurrence Reduction	**4%**			
Discontinued/Not eligible	36		32	
Imputed data	12		6	
Lost to or no F/U	8		6	
Adverse event (patients/AEs)	30/39		11/15	
Severe or life threatening AEs	7 B		1 W	

B = Azotemia, cardiac death, esophageal CA, AA rupture, pneumonia, hematuria, lung CA
W = bladder hemorrhage

Thus the primary detection analysis data from Trial 305 demonstrated efficacy at 99% C.I. for detecting significantly more Ta and T1 bladder tumors by blue light than by white light cystoscopy. Whereas, the reduction in early follow-up detection data supported clinical meaningfulness for detection, the data did not demonstrate statistical significance from Trials 305 and 304.

Analysis Populations

Initial Detection Criteria

The detection primary efficacy analysis in Trial 305 (ITT set) consists of all patients who:

1. Were randomized to Hexvix cystoscopy
2. Received Hexvix instillation
3. Had cystoscopic exam under WL and BL
4. Not a "training" patient
5. Central Pathology histologically-confirmed Ta or T1 result from at least one biopsy

The detection primary efficacy analysis in Trial 305 (PP set) consists of all patients who fulfilled the criteria for inclusion in the detection ITT analysis set and did not meet any of the following exclusion criteria:

1. Failed to fulfill eligibility criteria but was still entered into the study
2. Had a protocol violation thought to affect the result of the first cystoscopy or the histological valuation
3. Failed to retain Hexvix solution for at least 30 minutes
4. Time from the Hexvix instillation to the start of the cystoscopic procedure was less than 45 minutes
5. Technical failure with blue light examination

Follow-up Detection "Recurrence" Criteria

For the recurrence primary efficacy analysis in Trial 305 (ITT set) the following inclusion criteria were used:

1. Local pathology histologically-confirmed Ta or T1 result from at least one cystoscopic biopsy

And the following exclusion criteria were used:

1. No Ta or T1 at baseline
2. No valid local pathology at baseline
3. T2 or higher stage at baseline
4. T1 and no smooth muscle in biopsies at baseline (invasion of lamina propria)

For the recurrence PP analysis, the following additional exclusion criteria were used:

1. Failure to fulfill criteria for inclusion in the recurrence ITT set
2. No follow-up data
3. Chemotherapy the same day or the day after TURB
4. Treatment with BCG that was not in accordance with the protocol

The PP analysis sets are used for supportive analyses of the primary efficacy endpoints to show if the exclusion of some patients from the ITT analysis set affected the overall conclusions of the primary efficacy results.

Subgroup analyses by sex (male, female), age category (<65 years and ≥65 years), and geographic location (United States, non–United States) were performed for the detection primary endpoint and recurrence primary endpoint analyses to help determine the effectiveness of Hexvix cystoscopy within these subgroups. Subgroup analyses based on race were not performed because of the predominantly white populations in the contributing studies.

Statistical Methods

FDA generally expects applicants to supply data from at least two adequate and well controlled clinical studies as confirmatory evidence of efficacy. However, FDA regards a single study as potentially sufficient if the supplied results are as persuasively robust as data from more than one study. Multiple considerations are involved in assessment of the data robustness, such as consistency of primary and secondary results, consistency of results among patient subsets, a relatively large patient sample size and strong statistical evidence of success.

The NDA applicant designed Study 305 with the intention of this single study providing robust evidence of Hexvix diagnostic efficacy. For example, the study used special design features intended to help ensure thorough white light cystoscopy among patients receiving Hexvix and validity of the pathology reads. Additionally, the applicant's statistical analytical plan identified success upon each of the study's co-primary endpoints as a p-value of less than 0.01.

The planned hypothesis to be tested for the initial detection primary endpoint (Trial 305) was Exact Test (two sided) as planned in the protocol and the Statistical Analysis Plan (SAP) and it was:

> π = Proportion of subjects in the Detection Endpoint Group who have at least one Lesion detected by Blue Light and not by White Light that was confirmed by Central Pathology to be Ta/T1.

Objective: To provide strong statistical evidence that:
$\pi > 10\%$ with significance level alpha = .01

Testing this hypothesis using an exact test gave a p-value < 0.001. The observed proportion of Hexvix group patients (Group B) who had at least one Ta or T1 tumor detected with Blue Light (BL) and not with White Light (WL) was 16%. Therefore, it was concluded that the proportion of patients where at least one additional Ta/T1 tumor was seen with BL (Group B) and not with WL (Group A) was larger than 10%. The CI was not used to make the claim that the proportion of patients who had Ta/T1 tumors seen in BL (Group B) and not in WL (Group A) was above 10%. The detection primary endpoint proportion was 16%, thus satisfying the success criteria.

The success criteria for the detection primary endpoint were discussed and agreed to with the FDA as part of the Special Protocol Assessment process for Protocol 305 and FDA's review of the SAP during the Type C Meeting held with the Division of Medical Imaging and Hematology Products on 15 February 2007.

The planned hypothesis to be tested for the follow-up detection endpoint was also two sided as planned in the protocol and SAP. The CMH test evaluated the association between the groups and the response variable given center as the stratification variable. A small p-value would imply a reduction in early follow-up detection. The CMH test was used to adjust for the center effect. Testing this hypothesis gave a p-value of 0.03 (success criteria < 0.01). The observed proportion of patients with recurrence within 9 months was 47% for BL (Hexvix - Group B) and 56% for WL (Group A), thus success was not achieved.

The follow-up detection component of the Trial 305 was compromised by approximately 40% (117/285) of subjects in each group with missing data (no follow-up, missing visit or data). This necessitated in a high proportion of recurrence results being imputed and counted as recurrences (**Table 15** :).

Table 15 : Contribution of Imputed Subjects to "Recurrence" Results - 305

	# Subjects	# Subjects Confirmed Recurrence	# Subjects Imputed Recurrence	# Subjects Recurrence
White Light Group	280	97 (35%)	60 (21%)	157 (56%)
Blue Light Group	271	71 (26%)	57 (21%)	128 (47%)

6.1.5 Analysis of Secondary Endpoints

Secondary Endpoints for Trial 305

Secondary efficacy variables included tumor detection rate, the proportion of patients with additional histologically confirmed lesions detected by Hexvix cystoscopy, the proportion of patients with lesions found by Hexvix only, false-positive detection rate, and the clinical usefulness of Hexvix cystoscopy. All secondary endpoint analyses were based on the SOT central panel read in Trial 305.

Tumor detection Rate

The total number of lesions of each specific type that were detected with either BL cystoscopy, WL cystoscopy or both was analyzed (**Table 16**). The detection rates were calculated for each of the following types of histological results: CIS; Ta; T1 and T2-T4. On a lesion level, Ta and T1 lesions were detected approximately equally by both WL and BL (80% of lesions detected by both, and 10% detected either by WL alone or by BL alone). T2-T4 lesions were easily detected by WL and BL only detected one additional lesion not seen by WL. A significant number of CIS lesions, 27/66 (41%) were detected by BL that were not visible by WL. Likewise, out of 160 dysplasia lesions, 73 (46%) were detected by both light sources, 29 (18%) only by WL and 58 (36%) only by BL. Detection of both dysplasia and CIS lesions benefited from the adjunct examination with Hexvix and BL cystoscopy.

Table 16 : **Lesion level for WL and BL Cystoscopy (Detection Secondary Endpoint) - 305**

Lesions N = 778	Hexvix Group N=365							
	CIS Lesions		Ta lesions		T1 lesions		T2-T4 Lesions	
Total	66		580		95		47	
By both	33 (50%)		472 (81%)		76 (80%)		38 (81%)	
WL only		6 (9%)		52 (9%)		10 (11%)		8 (17%)
BL only	27 (41%)		56 (10%)		9 (9%)		1 (2%)	

Patient Detection Rate

Proportion of patients with at least one confirmed specific type lesion detected with either BL or WL cystoscopy according to the SOT central panel read for Trial 305 is demonstrated in **Table 17**. On a patient level, 41/262 (16%) with Ta lesions, 8/63 (13%) with T1 lesions and 19/41 (46%) with CIS lesions had one or more lesions detected by BL cystoscopy.

Table 17 : **Patient Level for WL and BL Cystoscopy (Detection Secondary Endpoint) - 305**

Patients N= 397	Hexvix Group N=365							
	CIS Lesions		Ta lesions		T1 lesions		T2-T4 Lesions	
Total	41		262		63		31	
WL ≥1 Lesion		28 (68%)		257 (98%)		57 (90%)		30 (97%)
BL ≥1 Lesion	19 (46%)		41 (16%)		8 (13%)		1 (3%)	

Patients with at Least One Lesion Detected by BL and Not by WL

Proportion of patients with at least one confirmed specific type lesion detected with BL cystoscopy and not by WL cystoscopy according to the SOT central panel read for Trial 305 is summarized in **Table 18**. Only 4 patients with Ta or T1 lesions and 13 patients with CIS lesions had one or more lesions detected by BL only and none detected by WL.

Table 18 : **Patient Level Detected by BL and Non-Detected by WL (Detection Secondary Endpoint) - 305**

Patients N=397	Hexvix Group N=365			
	CIS Lesions	Ta lesions	T1 lesions	T2-T4 Lesions
Total	41	262	63	31
BL only ≥1 Lesion None WL	13 (32%)	4 (1%)		0

False Detection Fraction

The number of visible lesions seen with cystoscopy that have a non-malignant histological result (excludes dysplasia, CIS, Ta, T1, T2, T3 and T4 lesions biopsied according to the SOT central panel read for Trial 305) divided by total number of visible lesions biopsied was considered as the false detection rate or fraction. The upper half of **Table 19** summarizes the false detection fractions calculated for each group based on the total of lesions biopsied by either light source. Across groups, the true positive fractions varied from 88% to 90%, while the false positive fractions were similar (11% for WL vs 12% for BL).

The lower half of Table 19 summarizes the false detection rate based on all lesions suspected by only a single light source, BL or WL. Analysis of all lesions suspected by only a single light source revealed that the false detection rate was numerically slightly higher (17% for WL vs. 23% for BL) when lesions are found only with blue light.

In this study, the false detection rate associated with WL cystoscopy was 11%. When WL cystoscopy was followed by BL and additional lesions were visualized with BL, 23% of those additional lesions detected only by BL were found to be non-cancerous or false positives.

A certain level of histologically negative biopsies is to be expected with standard cystoscopy examinations when suspecting a cancerous bladder. However, biopsies that do not yield significant pathology need to be considered as safety risks because each one can result in hemorrhage, infection, perforation or fistula formation. An increased incidence of false-positive histology during fluorescence cystoscopy has been linked to biopsies of areas of: 1) general inflammation, 2) former resection because of inflammatory changes and 3) intravesical therapy (chemotherapy and BCG) that causes

inflammation. The risk of false-positive lesions being biopsied during a cystoscopic examination needs to be balanced with the risk of missing out on the detection of additional cancerous lesions.

Table 19 : False Detection Rates - 305

False Detection Fraction Based on Lesions Suspected by Either Light		
Lesions	**Hexvix Group N = 1,090**	
	White Light	**Blue Light**
Number lesions suspected	**917**	**988**
Negative pathology	**97**	**120**
False detection rate	**11%**	**12%**
False Detection Fraction Based on Lesions Suspected by Only One Light		
Lesions	**Hexvix Group N = 323**	
	White Light	**Blue Light**
Number lesions suspected	**126**	**197**
Negative pathology	**21**	**46**
False detection rate	**17%**	**23%**

Clinical Usefulness of Hexvix

The clinical usefulness of Hexvix cystoscopy was measured as the proportion of patients for whom the investigator found Hexvix useful for a) diagnosing and b) deciding on further treatment of the patient. Investigators in Trial 305 found that Hexvix BL cystoscopy used as an adjunct to WL cystoscopy was useful in diagnosing papillary bladder tumors (73%) and for deciding further patient management (57%) as demonstrated in **Table 20**.

Overall, the study populations and clinical study results presented are representative of how Hexvix cystoscopy will be utilized in clinical practice and the results that will be expected from the procedure following approval.

Table 20 : **Investigator's Assessment of Clinical Usefulness of Hexvix (Secondary Endpoint) – 305**

Question	Statistic/ Response	Hexvix Group N =365	
Did you find Hexvix cystoscopy to be useful in diagnosing bladder tumors as an add-on procedure to white light cystoscopy?	**Number of Observations**	**361**	
		Yes	**No**
		263 (73%)	**98 (27%)**
	95% Exact CI	**(68-77)%**	
Did you find Hexvix cystoscopy to be useful for deciding further patient management?	**Number of Observations**	**359**	
		Yes	**No**
		203 (57%)	**156 (44%)**
	95% Exact CI	**(52-62)%**	

Comparison of Number of Patients with 0, 1, 2 or 3 Ta or T1 Lesions Seen with BL or WL within Hexvix Group

Among the 286 patients with abnormal central pathology reads, there was generally agreement on the number of patients with 0, 1, 2, or 3 or more Ta or T1 bladder lesions detected by WL and BL within the Hexvix group. In fact, in 226/286 patients (79%) there was numerical agreement on the number of lesions (0, 1, 2, or 3 or more lesions) per patient. Only 4 patients had lesions detected by BL where none were detected by WL cystoscopy. However, 23 patients with Ta or T1 lesions were detected by WL where none were detected by BL (11 with 1 lesion, 7 with 2 lesions and 5 with 3 or more lesions). Therefore, it will be important to include in the prescribing label that evaluation of the bladder for malignant lesions can not be performed by BL cystoscopy alone. BL cystoscopy must always be performed as an adjunct to WL cystoscopy. See **Table 21**.

Table 21 : **Comparison of Number of Patients with 0, 1, 2 or 3 Ta or T1 Lesions Seen with BL or WL within Hexvix Group (Secondary Endpoint) - 305**

Central Pathology Reads Patients N=286	Number of Lesions	Ta or T1 Lesions Detected by BL			
		0	1	2	≥3
Ta or T1 Lesions Detected by WL	0	**0**	3	0	1
	1	*11*	**91**	10	2
	2	*7*	2	**60**	14
	≥3	*5*	2	3	**75**

Efficacy in Subpopulations

Subgroup analyses by sex (male, female), age category (<65 years and ≥65 years), and geographic location (United States, non–United States) were performed for the detection primary endpoint to help determine the effectiveness of Hexvix cystoscopy within these subgroups. Subgroup analyses based on race were not performed because of the predominantly white populations in the contributing studies. For the sex subgroup analysis of the primary detection endpoint, more females than males had at least one Ta or T1 lesion seen in blue light that was not seen in WL. However, the ratio of males to females across studies was approximately 3:1 to 4:1 and this imbalance may render the analysis in the female population less reliable. Similarly, no obvious differences in the primary detection endpoint with respect to age were observed, and results of the age group analysis were also variable. This variability is likely related to the imbalance in the two age subgroups; there were on average two to three times as many patients in the 65-years-or-older age group than in the under-65-years age group. These demographic differences are expected and are reflective of the general population affected by bladder cancer.

In the recurrence segment of Study 305, the follow-up detection reduction was numerically higher in females in the Hexvix BL group (“recurrence” 39% in BL vs. 63% in WL group)(lower proportion of participants than males) and among males over 65 years of age (**Table 22**).

Table 22 : **"Recurrence" Endpoint by Sex & Age - 305 (ITT Set)**

	Hexvix N =271			WL N = 280			Relative Recurrence Reduction (99% CI)
	Number Recurrences	Non-Missing Observations	Recurrence Rate (%) (99% CI)	Number Recurrences	Non-Missing Observations	Recurrence Rate (%) (99% CI)	
Sex							
F	23	59	39 % (23-57)	36	57	63 % (45-79)	38 % (-1, 62)
M	105	212	50 % (41-59)	121	223	54 % (45-63)	9 % (-6, 28)
Age							
>65	79	168	47 % (37-57)	106	184	58 % (48-67)	18 % (-7, 38)
≤ 65	49	103	48 % (35-61)	51	96	53 % (40-66)	11 % (-29,38)

Efficacy by Geographic Location

Among the 47 patients with at least one Ta or T1 lesion seen by blue light that was not seen by WL, the proportion of patients in the United States sites was approximately twofold greater than in the non-US sites (**Table 23**). Also, there were more patients with recurrent cancer at baseline in the United States than in European sites. Whereas the overall improved detection rate was 16%, the data results were driven by the performance at the United States sites, 24% versus 11%.

Table 23 : Efficacy by Geographic Location 305 (ITT) - (Secondary Endpoint)

Patient Detection Rate		
Patients with ≥ 1 confirmed Ta or T1 tumor	**U.S. 121**	**Non-U.S. 165**
Patients with ≥ 1 confirmed Ta or T1 tumor detected with BL but not by WL	**16%**	
	29 24%	**18 11%**
95% CI	**(17-33)**	**(7-17)**
p-value	**<0.001**	**0.771**

Secondary Endpoints for Trial 304

False Detection Fractions on Patient and Lesion Level

While the lesion based false detection rate in Trial 305 was 11% for white light and 12% for blue light, in Trial 304 the rates were considerably higher in most groups (**Table 24**). The highest false detection rates were observed within the Hexvix plus blue light cystoscopy group, 36% among patients with suspected lesions and 55% among lesions with suspected biopsied pathology. The number of visible lesions seen with cystoscopy that have a non-malignant histological result (according to the local pathology read for Trial 304) divided by total number of suspected visible lesions biopsied was considered as the false detection rate or fraction. True positive detection fractions and false detection fractions were calculated by patients and by lesions for each group, Hexvix plus BL, Hexvix plus WL and white light only. Across groups, the true positive fractions on a patient level were variable: 64% for Hexvix plus BL, 92% for Hexvix plus WL and 84% for white light only groups. The false positive fractions on a patient level were also variable: 36% for Hexvix plus BL, 8% for Hexvix plus WL and 17% for white light only groups.

On a lesion level, the true positive fractions were lower: 45% for Hexvix plus BL 70% for Hexvix plus WL groups and 68% for white light only; the false positive fractions were higher: 55% for Hexvix plus BL, 32% for white light only and 30% for Hexvix plus WL groups. In this trial the false detection fraction was higher for the Hexvix plus BL group in both the patient (36%) and lesion level (55%) assessments.

Before all subjects were examined with blue light, they had previously undergone cystoscopic biopsy/resection with white light. It is known that prior resection can induce inflammatory changes in the bladder epithelium and all patients evaluated by BL cystoscopy in this trial had prior biopsy/resection under WL. Performance of TURB under WL before examining with BL probably contributed to distortion of the bladder anatomy and probably contributed to the higher false detection rates. Therefore, it will be necessary to include this information in the prescribing label for the benefit of urological cystoscopists.

Table 24 : False Detection Fractions in Trial 304

False Detection Fraction Based on Patients with Suspected Pathology			
Patients with:	***Hexvix Group N=102***		***WL Group N=117***
	Blue Light	**White Light**	**White Light**
Suspected lesions	**69**	**95**	**115**
Negative pathology	**25**	**8**	**19**
False detection rate	**36%**	**8%**	**17%**
False Detection Fraction Based on Suspected Pathology Biopsied			
Lesions	**Blue Light**	**White Light**	**White Light**
Number lesions suspected	196	210	232
Negative pathology	108	**63**	**75**
False detection rate	**55%**	**30%**	**32%**

Patients with Tumor Detection Rate

The total number of patients with each specific type of tumor detected with either BL cystoscopy or WL cystoscopy was analyzed (**Table 25**). Patients were calculated with each of the following types of histological results: hyperplasia, dysplasia, CIS, Ta, T1 and T2-T4. On a patient level, more patients with hyperplasia, dysplasia and CIS had their lesions detected by BL cystoscopy while more patients with Ta, T1 and T2-T4 had their lesions detected by WL cystoscopy.

Table 25 : Number of Patients with Lesions Detected at Baseline for Different Tumor Types – 304 (ITT Set)

Total Patients with Lesions Detected	Hyperplasia		Dysplasia		CIS		Ta		T1		T2-T4	
	4		24		5		83		8		5	
WL N = 117		0		7		2		79		7		5
BL N = 102	4		20		4		34		3		0	

Detection Analyses of Supportive Studies

Even though assessment of the Ta and T1 detection rate was not an objective of the supportive studies, patients within these studies did undergo both white and blue light examinations such that detection rates can be summarized. **Table 26** shows the four major supportive studies with the number of patients with any Ta or T1 lesions detected by either white and/or blue light from each study. In these supportive studies, the percent of patients with any Ta or T1 lesions detected only by blue light ranged from 19 to 42%. However, we must remember that these studies were not designed to optimize the thoroughness of the white light cystoscopy, the pathological examinations were not well standardized and all these analyses are of a post-hoc nature.

Table 26 : Exploratory Detection Analyses of Supportive Studies

Patients with	Study			
Ta or T1 lesions	304 n = 86	303 n = 75	302 n = 121	301 n = 154
Ta or T1 lesions Seen only by BL	42%	19%	29%	27%

Summary of Detection Analyses

Overall, the total number of lesions detected during cystoscopy was consistently higher with Hexvix blue-light cystoscopy compared with WL cystoscopy, and improved detection of malignant and premalignant lesions with Hexvix cystoscopy was demonstrated. Detection rates were different depending on lesion type regardless of light mode used, blue light or WL. Rate differences between cystoscopic methods were greatest for dysplasia and CIS lesions, with higher detection rates observed for these lesions after blue-light cystoscopy compared with WL cystoscopy across all studies. The

detection rates for Ta and T1 tumors were similar for blue-light cystoscopy and WL cystoscopy in both Studies 305 and 304; however, in Study 305, the detection rate for T2-T4 tumors was lower with blue-light cystoscopy than with WL cystoscopy

Similar to the detection rate finding, the proportion of additional lesions identified with Hexvix cystoscopy varied according to lesion type; the most additional lesions were found for flat lesions (CIS and dysplasia), and the least were found for T2-T4 lesions. In Study 305, the proportion of patients with at least one additional lesion of the same type detected with Hexvix cystoscopy, but not with WL cystoscopy, was 13% for T1 lesions, 16% for Ta lesions, 3% for T2-T4 lesions and 46% for CIS lesions.

The findings above are important for several reasons. For Ta and T1 lesions, the detection of further tumors allow a more precise and complete resection to be carried out. A more complete resection decreases the chances of tumor recurrence; this is particularly important for T1 tumors, which have a high rate of recurrence and progression.

6.1.6 Other Endpoints

Detection Efficacy Results Based on Population Size of Trial Centers

During the selection process of Centers for DSI site inspection, an association was observed between the population size of study sites and the efficacy results. **Table 27** displays those sites with the largest number of patients with Ta and T1 lesions. These trial centers, each with $\geq$ 23 patients with Ta or T1 lesions, had the lowest detection rates for number of patients with more lesions detected by BL than WL (range 0% to 22%). From the 125 patients in this group, only 10 patients were among the 47 (21%) patients that had one or more Ta or T1 lesions detected by BL than WL. Because the detection rates were lowest at these trial sites, none were selected for DSI site visits.

Table 27 : Centers with Largest Number of Patients with Ta or T1 Papillary Tumors - 305

Trial Centers N = 28	Center Locations	Number Patients Ta or T1	Number Patients BL>WL
Sites with Largest Number of Ta or T1 Patients Number in Hexvix Group with Ta or T1 Lesions = 278			
304	Germany	30	1 (3%)
201	Canada	26	0 (0%)
11	Rochester	23	5 (22%)
301	Germany	23	2 (9%)
302	Germany	23	2 (9%)
Sites Not Selected for DSI		**BL>WL Patients**	**10/47 (21%)**

Six Center sites with $\leq$ 23 patients with Ta or T1 lesions had the highest detection rates for number of patients with more lesions detected by BL than WL (range 29% to 75%) See **Table 28.** From the 87 patients in this group, 29 patients were among the 47 (62%) patients that had one or more Ta or T1 lesions detected by BL than WL. Because the detection rates were highest at these trial sites, DSI site visits were selected from among this group.

These results suggest that the highest detection rates among patients with Ta or T1 lesions that had more lesions detected by BL than WL were found at the sites with smaller populations.

Table 28 : Centers with Largest Number of Patients with BL>WL Ta or T1 Papillary Tumors - 305

Trial Centers N = 28	Center Locations	Number Patients Ta or T1	Number Patients BL>WL
Sites with Largest Number of BL>WL Patients Number of BL>WL Ta or T1 Patients = 47			
8	**Philadelphia**	8	**6 (75%)**
11	Rochester	23	5 (22%)
16	Miami	19	5 (26%)
403	**Netherlands**	12	**5 (42%)**
10	**Rochester**	11	**4 (36%)**
402	Netherlands	14	4 (29%)
Bolded Sites Selected for DSI		**BL>WL Patients**	**29/47 (62%)**

Follow-up Detection by Tumor Type

As displayed. In **Table 29**, the proportion of patients with available follow-up detection pathology was comparable between study groups, Hexvix group (65%) and WL group (64%). A number of patients in both study groups did not have follow-up pathology and were imputed to recurrence to give a total of 128 and 157 recurrences within 9 months for the Hexvix group and WL group, respectively. Ta lesions at baseline contributed to 75% (580/778) of the abnormal pathology lesions detected within the Hexvix group. Similarly in the Hexvix group, the majority of abnormal pathology lesions detected at follow-up was Ta from Ta at baseline, 76% (63/83).

Table 29 : Recurrence by Tumor Type (Study 305) ITT

Worst type at baseline	Worst type at follow-up	Hexvix (Blue Light) N = 271 n	WL N = 280 n
TX	TX	-	1 (0.6%)
Ta	CIS	2 (1.6%)	2 (1.3%)
Ta	Ta	63 (49.2%)	70 (44.6%)
Ta	T1	5 (3.9%)	7 (4.5%)
Ta	T2	2 (1.6%)	4 (2.5%)
T1	CIS	-	3 (1.9%)
T1	Ta	7 (5.5%)	6 (3.8%)
T1	T1	1 (0.8%)	5 (3.2%)
T1	T2	2 (1.6%)	3 (1.9%)
T1	T3	1 (0.8%)	-
Number of observations		83 (64.8%)	101 (64.3%)
Total with recurrence		128	157

Percentages are based on the total number of recurrences. TX = lesion cannot be staged

7 Review of Safety

Safety Summary

Overall, 1,324 patients received bladder instillation of Hexvix in the six controlled clinical trials. Adverse events (AEs) were assessed from the time of Hexvix instillation until exit from the study; treatment-emergent adverse events (TEAEs) were events that occurred or worsened after exposure had begun.

Overall, 17 (1%) Hexvix-cystoscopy patients and 4 (1%) WL-cystoscopy patients died during the Hexvix clinical development program. None of the fatal outcomes were judged to be related to the study drug. Overall, 98 (7%) Hexvix-cystoscopy patients experienced at least one serious adverse event (SAE), which was similar to the proportion of SAEs in patients receiving only WL cystoscopy (36 patients, 7%). The most commonly observed SAEs were in the body system of renal and urinary disorders, particularly hematuria and urinary retention (most resolved before completion of the study). Overall, 12 (1%) Hexvix-cystoscopy patients enrolled in controlled Hexvix clinical studies were discontinued from the study early because of an AE. None of these SAEs were considered to be related to Hexvix exposure.

The most frequently reported AEs in Hexvix studies occurred in the renal and urinary disorders body system, a result that is consistent with the common symptoms and AEs associated with bladder cancer surgery and related to the administration of anesthesia and performance of cystoscopic TURB. They include: hematuria (16%), procedural pain

(9%), dysuria (9%), bladder spasm (6%), urinary retention (5%), bladder pain (4%), urinary tract infection (4%) and frequency (4%). The next highest incidence of AEs were: nausea and vomiting (5%), abdominal pain (3%) and headache (3%), all post-procedural complications that could be associated with cystoscopic surgery.

Most of these AEs were mild-to-moderate in severity and regarded as not related to exposure group, but rather were attributed to the underlying disease, ongoing medical conditions, or the surgical procedure. The majority of systemic AEs resulting from laboratory changes were consistent with complications associated with cystoscopy. There was no indication that Hexvix adversely affected clinical hematology and serum chemistry parameters.

In general, data provided no indication that Hexvix adversely affected vital signs and physical examination findings.

Similar patterns of adverse events were noted within Study 305 and all the controlled studies, with no difference between the Hexvix blue light and white light groups in the nature or number of events.

During the Hexvix postmarketing surveillance period through September 2009, isolated SAEs of anaphylactic shock, vascular purpura with cutaneous necrosis and pruritis have been reported among patients exposed to Hexvix.

7.1 Methods

Cystoscopic examination of the bladder, including biopsy, constitutes the gold standard for diagnosis and surveillance in bladder cancer. This can be done using rigid or flexible instruments. It uses a telescope equipped with a camera inserted through the urethra into the bladder. The choice of telescope, differing in flexibility and diameter, depends on the purpose of the examination. Flexible cystoscopy is used in outpatient clinics or office based cystoscopy examinations with local anesthesia. Rigid cystoscopy is used in an operating room under general anesthesia, due to the discomfort, particularly in male subjects, caused by the rigid scope. The rigid cystoscope is more commonly used for taking biopsies and tumor resection and was used in Hexvix clinical program for cystoscopic examinations

As with any invasive surgical procedure, cystoscopy involves certain risks. Cystoscopy commonly includes the use of anesthesia and sedatives, and the introduction of a catheter. The use of endoscopes and resectoscopes is included for removal of tumor by transurethral resection of the bladder (TURB), taking biopsies, and coagulation of blood vessels. Post-operative complications of rigid cystoscopy may include abnormal bleeding after biopsy, pain, and painful urination (secondary to urinary tract infection).

The procedure increases the risk of the following: urinary tract infection; bacteremia with or without sepsis; bladder perforation or other trauma to the bladder or urethra; postoperative pain; urine retention; and other less frequent complications. Also, bladder spasm can occur when the bladder is irritated by the presence of the urinary catheter or in connection with chronic bladder disorders. These underlying conditions and the known risks involved with cystoscopy are expected and contribute, significantly in some cases, to the incidence and frequency of adverse events (AEs).

Fluorescence cystoscopy with Hexvix, depends upon the accumulation of porphyrins (fluorescing compounds that emit red light upon excitation by blue-light) primarily in neoplastic tissue which allows better visualization of suspicious tumor tissue. Based on the local route of administration as well as the short duration of exposure, use of Hexvix is not expected to contribute significantly to the AEs associated with WL cystoscopy. However, it is anticipated that patients may undergo repeated TURB with Hexvix as tumor recurrence is common. Whereas tumor recurrence is evaluated at follow-up visits at regular time intervals (typically every 3 months), it is therefore expected that there will be repeat examinations (instillation of Hexvix and urothelial exposure to blue light) at intervals of at least 3 months or longer between each exposures. From a safety point of view, it is reasonable to consider Hexvix as a single-use product. Data are not available to establish safe guidelines for repetitive usage.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Overall, 1,324 patients received bladder instillation of Hexvix in the six controlled clinical trials. The clinical safety database comprises all patients enrolled in studies 201, 301, 302, 303, 304, and 305 who received Hexvix solution (patients with or suspected of having superficial bladder cancer) and had any post baseline safety data recorded (**Table 30**). These studies were multinational, two- or multicenter, open-label, within-patient controlled, comparative efficacy trials comparing Hexvix BL cystoscopy with WL cystoscopy in the detection of bladder cancer. Safety data for Hexvix patients receiving a single instillation of Hexvix which was retained for approximately 1 hour in the bladder included 1,324 patients, aged 32 to 96 years with a median age of 69 years. Patients in all studies were primarily elderly, white and male. The male to female ratio was approximately 3:1. Across all clinical studies, the patient population consists of mostly elderly men and women with comparable age and baseline characteristics.

Table 30 : Hexvix Exposure in 6 Controlled Trials –Safety Set

	Numbers %
Patients in controlled trials *	**1,356**
Patients received Hexvix	**1,324 (98%)**
Patients received Hexvix + cysto	**1,261 (93%)**

* Studies 305, 304, 303, 302, 301, 201

Many patients undergoing diagnostic procedures and treatment for bladder cancer have multiple co-morbidities for which additional concomitant medications were prescribed. Across all controlled studies, 87% of patients in the Hexvix study group and 73% of patients in the WL study group suffered from ongoing diseases, as compared with 93% of Hexvix-cystoscopy patients in Pool "Total." For example, cigarette smoking is the single greatest risk for bladder cancer and also predisposes patients to cardiovascular and pulmonary diseases. The most common symptom of bladder cancer is hematuria, which occurs in 80% to 90% of patients. Other less frequent signs may include urinary frequency, difficulty or pain in urination (dysuria), pelvic pain, and a range of other renal or urinary tract–related problems that could also be age-related co-morbidities.

The underlying conditions of an elderly patient population and complications involved with the surgery and the anesthesia in connection with the cystoscopic procedure complicated the clinical condition of these elderly patients. Indeed, patients included in the clinical program used a number of concomitant medications in addition to those associated with the cystoscopy procedure itself. Nearly all patients in the Hexvix study group and the WL study group took concomitant medications; most of these medications were expected, given an older population, with a malignant disease and undergoing a cystoscopic procedure.

Safety data from the six controlled clinical studies in patients with or suspected of having non–muscle invasive bladder cancer were provided to support that Hexvix can be safely administered to this patient population. Safety data collected during the Hexvix cystoscopy clinical development program were similar across studies. As agreed upon with the FDA, the integrated safety database for this NDA includes baseline data and safety data as follows:

- Exposure
- Demographics and baseline disease characteristics (bladder evaluations, bladder cancer history, and prior and concomitant medications)
- Common adverse events (AEs) (≥1%), related AEs (reported in ≥2 patients), AEs related to study product, summary of patients' deaths, serious adverse events (SAEs), AEs leading to discontinuation, and AEs based on laboratory changes
- Clinical laboratory evaluations (hematology and biochemistry)
- Physical examinations and vital signs

Table 31 summarizes the safety evaluations performed by study.

Table 31 : Safety Evaluations Performed by Study

Evaluations	PC B201/00	PC B301/01	PC B302/01	PC B303/01	PC B304/04	PC B305/04
Adverse events*	X	X	X	X	X	X
Hematology and biochemistry†	X	X	X			
Vital signs‡		X	X	X		X
Physical examination‡		X	X	X		X
Concomitant medications‖	X	X	X	X	X	X

Adverse events (AEs) were assessed from the time of Hexvix instillation until exit from the study; treatment-emergent adverse events (TEAEs) were events that occurred or worsened after exposure had begun. For patients in Study 305 and Study 304 who were randomized to the standard cystoscopy arms, TEAEs were events that occurred or worsened after the initiation of the standard cystoscopy procedure. In Study 305, TEAEs was assessed from Hexvix instillation and initial cystoscopy procedure until 30 days after exposure (according to second protocol amendment).

In Study 304, TEAEs were assessed from the time of enrollment through the 12-month follow-up visit. In the earlier Hexvix studies, patients were followed for at least 7 days after exposure in the Studies 301, 302, and 303, and in the Study 201, patients were followed for 3 months after exposure or until administration of pharmacological treatment. AEs considered by the investigator to be related to Hexvix or WL with a high degree of certainty or AEs having an uncertain relationship (i.e., all AEs, where a relationship to Hexvix or WL could not be ruled out) are presented together as “related AEs.”

The demographic characteristics for the safety patient population for Study 305 are displayed in **Table 32**.

Table 32 : Demographic Characteristics - Safety Patient Population 305

	Hexvix Group				White Light Group			
	N	Mean	SD	Range	N	Mean	SD	Range
Age (years)	**421**	**68**	**11**	**39-96**	**381**	**70**	**11**	**24-94**
Gender **Male** **Female**	**421** **322** **99**				**381** **301** **80**			
Childbearing potential **No**	**102** **95**				**84** **84**			
Weight (kg)	**417**	**83**	**17**	**42-136**	**380**	**83**	**18**	**50-154**
BMI (kg/m2)	**416**	**28**	**5**	**18-47**	**380**	**28**	**5**	**17-46**
Ethnic group **White** **Black** **Asian** **American** **Hispanic Other**	**421** **386** **11** **3** **5** **16**				**381** **364** **5** **1** **4** **7**			

An overview of the adverse events in Study 305 and 304 are summarized in **Table 33** and **Table 34 ,** respectively**.** Further details follow.

Table 33 : Overview of Adverse Events - 305 Safety Set

Adverse Events	Hexvix BL N = 421			WL N = 381		
	Episodes	Number Patients	% Patients	Episodes	Number Patients	% Patients
Overall incidence	562	202	48%	476	193	51%
Treatment-related	50	33	8%		0	0%
Led to discontinuation	1	10	2%	1	1*	<1%
SAEs	51	39	9%	39	32	8%
SAEs – Rx related	2	2 **S**	<1%		0	0%
Deaths	5	5	1	4	4	1

S = 1 Urinary retention, 1 bladder spasm

Table 34 : Overview of Adverse Events - 304 Safety Set

Adverse Events	Hexvix BL N = 112			WL N = 118		
	Episodes	Number Patients	% Patients	Episodes	Number Patients	% Patients
Overall incidence	39	30	27	15	11	9
Treatment-related	7	6	5	1	1	1
Led to discontinuation	4	4	4	0	0	0
SAEs	13	12 B	11	7	4 W	3
SAEs – Rx related	0	0	0	0	0	0
Deaths	5	5 D	5	0	0	0

B = 5 Deaths, 4 urinary retention, 1 post-procedure hematuria, 1 lung malignancy, 1 cystitis & urinary retention
W = 1 Each bladder hemorrhage, hematuria, temporary catheter, 1 patient with anxiety, hypertension, hematuria & back pain
D = 1 Each azotemia, esophageal CA, AA rupture, pneumonia & cardiac death

7.1.2 Categorization of Adverse Events

The most frequently reported AEs in Hexvix studies occurred in the renal and urinary disorders body system, a result that is consistent with the common symptoms and AEs associated with bladder cancer surgery and related to the administration of anesthesia and performance of cystoscopic TURB. They include: hematuria (16%), procedural pain (9%), dysuria (9%), bladder spasm (6%), urinary retention (5%), bladder pain (4%), urinary tract infection (4%) and frequency (4%). The next highest incidence of AEs were: nausea and vomiting (5%), abdominal pain (3%) and headache (3%), all post-procedural complications that could be associated with cystoscopic surgery. Most of these AEs were mild-to-moderate in severity and regarded as not related to exposure group, but rather were attributed to the underlying disease, ongoing medical conditions, or the surgical procedure.

Overall, 98 (7%) Hexvix-cystoscopy patients experienced at least one serious adverse event (SAE), which was similar to the proportion of SAEs in patients receiving only WL cystoscopy (36 patients, 7%). The most commonly observed SAEs were in the body system of renal and urinary disorders, particularly hematuria and urinary retention (most resolved before completion of the study). The next most frequent SAEs were cardiac disorders including chest pain and tachycardia, and then infections and sepsis. These results are consistent with disease-related complications of cystoscopy often experienced by elderly patients during evaluation for bladder cancer.

The most frequently reported AEs in Hexvix studies occurred in the renal and urinary disorders body system, a result that is consistent with the common symptoms and AEs associated with bladder cancer surgery and related to the administration of anesthesia and performance of cystoscopic TURB. They include: hematuria (16%), procedural pain (9%), dysuria (9%), bladder spasm (6%), urinary retention (5%), bladder pain (4%), urinary tract infection (4%) and frequency (4%).

The next highest incidence of AEs were: nausea and vomiting (5%), abdominal pain (3%) and headache (3%), all post-procedural complications that could be associated with cystoscopic surgery.

Most of these AEs were mild-to-moderate in severity and regarded as not related to exposure group, but rather were attributed to the underlying disease, ongoing medical conditions, or the surgical procedure.

There were 5 deaths reported in each Hexvix treatment group (Studies 305 and 304) that were considered not related to Hexvix or the study procedures.

Table 35 summarizes the SAEs observed in Study 305; **Table 36** summarizes the most frequent SAEs observed in safety set of Study 305.

In Study 305, a total of 39 (9%) patients had 51 SAEs in the Hexvix group and 32 (8%) patients had 39 SAEs in the white light group. The most common SAEs were haematuria (5 [1%] patients in the Hexvix group; 4 [1%] patients in the white light group), followed by urinary retention (2 [0.5%] patients in the Hexvix group; 4 [1.0%] patients in the white light group). One SAE (mild bladder spasms) was assessed to be of uncertain relationship to Hexvix. All of the other SAEs were not treatment-related.

Table 35 : Summary of SAEs 305 - Safety Set

System Organ Class MedDRA preferred Term	Hexvix Group n=421		WL Group n=381	
Total number of SAEs	51		39	
Number Patients with ≥1 SAE	39	9%	32	8%
Renal and urinary disorders	9	2%	12	3%
Cardiac disorders	8	2%	8	2%
Infections and infestations	4	1%	1	<1%
Neoplasms	4	1%	1	<1%
Reproductive	3	1%	1	<1%
Respiratory, thoracic, mediastinal	2	1%	0	0
Surgical & medical procedures	3	1%	3	1%
Injury, procedural complications	2	1%	2	1%
Musculoskeletal, connective tissue	2	1%	1	<1%
Psychiatric disorders	2	1%	0	0
Vascular disorders	2	1%	1	<1%

Table 36 : Most Frequent SAEs 305 - Safety Set

	Hexvix Group N = 421		WL Group N = 381	
Patients with SAEs/Total SAEs	n=39	N = 51	n=32	N = 39
Renal & urinary disorders	9	2 %	12	3 %
Hematuria	5	1	4	1
Urinary perforation	2	1	4	1
Bladder perforation	0	1	1	<1
Bladder tamponade	0	0	2	1
Urinary bladder hemorrhage	0	0	1	<1
Bladder spasm	1	<1	0	0
Hemorrhage urinary tract	1	<1	0	0
Hydronephrosis	1	<1	1	<1
Cardiac disorders	8	2 %	8	2 %
Atrial fibrillation	2	1	1	<1
Cardiac failure congestive	2	1	0	0
Myocardial infarction	2	1	3	1
Coronary artery disease	0	0	1	<1
Angina pectoris	1	<1	3	1
Nodal arrhythmia	1	<1	0	0

In Study 304, five (5%) patients in the Hexvix cystoscopy group died. None of the deaths or SAEs were considered to be treatment-related. There were no adverse events or SAEs that led to withdrawal from the study additional to the patients who died.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The IAS of this NDA is based on six controlled studies and the “safety set” refers to all patients included in Studies 201, 301, 302, 303, 304, and 305 who received Hexvix solution or WL cystoscopy and had any post baseline safety data recorded. As

agreed upon in the Type B meeting with the FDA held on 24 February 2009, the safety data from the registration Study 305 and the supportive Study 304 have been pooled and are designated as "304/305" data. Supportive safety data from patients instilled with Hexvix in Studies 201, 301, 302, and 303 also have been integrated with new Studies 305 and 304 for an "Overall" analysis of patients exposed to Hexvix. Integrated supportive safety data from NDA (b) (4) (designated as "Total") have been presented in this Summary of Clinical Safety. As previously mentioned, the "Total" data has been reanalyzed for the purpose of this submission.

A summary of all AEs leading to study discontinuation, not including death unless it was reported as an AE, is presented by relationship to study procedure in **Table 37**.

Table 37 : Summary of Adverse Events Leading to Discontinuation – Safety Set

MedDRA Preferred Term	Hexvix N = 1,324 Overall			
	Related	Uncertain	Not related	Sum
Total number of AEs	0	2	10	12
Patients with ≥ 1 AE	0	1	10	11 (1%)
Cardiac arrhythmia	0	1	1	2
Pneumonia	0	0	2	2
Death	0	0	2	2
Chest pain	0	1	0	1
Azotemia	0	0	1	1
Urethral perforation	0	0	1	1
Esophageal cancer	0	0	1	1
Urinary bladder excision	0	0	1	1
Malignant hypertension	0	0	1	1

7.2 Adequacy of Safety Assessments

The safety assessment focused on the aged population, those at higher risk for bladder cancer. This group of patients has a higher incidence of concomitant disease states and generally a higher consumption of prescription drugs which increased the possibility for adverse events, both related and not related to the study drug. The Hexvix exposed data base of over 1300 patients is adequate.

7.2.1 Overall Exposure at Appropriate Doses/Durations

Based on the route of administration (intravesical), limited systemic absorption and rapid degradation upon contact with blood, the risk for potentially interfering pharmacokinetic interactions with other drugs seems to be minimal.

Durations of Cystoscopic Examinations

The cystoscopic examinations performed in Trial 305 were video-taped according to the protocol of the study, and these tapes have been used to obtain data about the duration of the cystoscopic examinations in white and blue light. A total of 43 such video tapes from the subset of patients where the settings were registered were analyzed. This constitutes 10 % of the total Hexvix safety population. The analysis of the video tapes was performed by a certified urologist in an imaging laboratory. The results provided describe the duration of the cystoscopic examinations including the resection of identified bladder lesions.

The mean durations of the bladder mapping were 4.7 minutes in white light and 3.2 minutes in blue light, ranging up to 15 and 13 minutes, respectively. The mean durations of light exposure, which includes both bladder mapping and resection were 13.6 minutes in white light and 5.0 minutes in blue light. The range for the total durations including resection was up to 36 minutes in white light and up to 11 minutes in blue light. The analysis identified that the individual blue light cystoscopy examinations were lengthier than the average examination.

There are 13 patients with illumination of at least 5 minutes in blue light, and adverse events were reported in five of these (38%). Overall 49% of the patients in the Hexvix group in study 305 reported adverse events. Thus, there does not seem to be any trend to support a hypothesis that there is a difference between these patients and the overall Hexvix patients in the subset of patients with the longest illumination with blue light. The cystoscopic procedure in Study 305 included white light and blue light mapping followed by resection in white light. The safety data presented here includes the additional light exposure during the resection of the lesions identified during the bladder mapping in white and blue light.

Possibility of Pathological Damage Associated with Hexvix Plus PDD Cystoscopy

According to the sponsor, the possibility of pathological damage by the use of the PDD systems marketed in Europe in combination with Hexvix has been evaluated as part of clinical studies and in routine clinical practice by an experienced pathologist; (b) (4) [redacted]. She has read thousands of biopsies taken during and after PDD of the bladder and reports that she has never observed any difference between urothelial specimens from patients examined with PDD after

installation of Hexvix compared to specimens from patients examined with white light only. These observations are based on the analysis of biopsies taken during the cystoscopic examination and also at follow-up (usually after 4-6 weeks or after 3 months, depending on the indication).

Postmarketing Safety Experience

During the Hexvix postmarketing surveillance period through September 2009, isolated SAEs of anaphylactic shock, vascular purpura with cutaneous necrosis and pruritis have been reported among patients exposed to Hexvix. (See Section 8)

7.2.2 Explorations for Dose and Duration of Bladder Instillation Response

In the exploratory study, Study 001, 91 patients with bladder cancer received HAL solution at concentrations up to 16 mM, which is twice the clinical use concentration; several patients had instillation times that exceeded 150 minutes, but no unexpected AEs occurred. In the compassionate-use program, 86 patients with known or suspected bladder cancer received one or more intravesical instillations of Hexvix 8 mM (50 mL); mean instillation time of Hexvix was 75 minutes (range: 30 to 215 minutes).

Study 103 evaluated the systemic absorption in healthy volunteers and found systemic bioavailability at 7% via bladder administration. No cases of overdose have been reported with instillation of twice the recommended concentration and prolonged instillation of 3 to 5 times the recommended time (3-5 hours).

The exposure data from 1,324 patients (mean retention time of the Hexvix solution was 88 minutes) support the intended labeling minimum time and maximum time for beginning the cystoscopic examinations of the bladder after instillation of Hexvix, which are 1 hour and 3 hours.

7.3 Major Safety Results

7.3.1 Deaths

Overall, 17 (1%) Hexvix-cystoscopy patients and 4 (1%) WL-cystoscopy patients died during the Hexvix clinical development program. None of the fatal outcomes were judged to be related to the study drug. Examples of deaths include: malignancies, myocardial infarction, congestive heart failure, pneumonia, azotemia, sepsis, aortic aneurysm rupture and asthenia. Time from instillation of Hexvix to death varied from 3 to 330 days (majority were over 60 days) (**Table 38** and **Table 39**).

Table 38 : Deaths Reported in Controlled Studies (Studies 201, 301, 302 and 303)

Group	Age	Sex	Time-to-Death	Cause of Death	Related
Study 201 (4)					
Hexvix	76	M	**78 Days**	**Lung squamous cell carcinoma**	NR
Hexvix	72	M	**69 Days**	**Acute myocardial infarction**	NR
Hexvix	93	F	**104 Days**	**Death**	NR
Hexvix	76	M	**30 Days**	**Metastases to bone**	NR
Study 301 (1)					
Hexvix	50	M	**25 Days**	**Metastases**	NR
Study 302 (1)					
Hexvix	83	F	**12 Days**	**Tachycardia**	NR
				Chest pain	NR
				Back pain	NR
				Aortic aneurysm	NR
Study 303 (1)					
Hexvix	57	M	**17 days**	**Pyrexia**	NR
			21 days	**Sepsis**	NR
			6 Days	**Cerebrovascular accident**	NR

NR = not related

Table 39 : Deaths Reported in Controlled Studies (Study 304 and 305)

Group	Age	Sex	Time-to-Death	Cause of Death	Related
Study 304 (5)					
Hexvix	92	M	**223 Days**	**Azotemia**	NR
Hexvix	82	M	**330 Days**	**Esophageal carcinoma**	NR
Hexvix	85	F	**61 Days**	**Aortic aneurysm rupture**	NR
Hexvix	96	M	**60 Days**	**Pneumonia**	NR
Hexvix	87	M	**144 Days**	**Cardiac death**	NR
Study 305 (9)					
W L	90	M	**208 Days**	**Death**	NR
W L	81	M	**195 days**	**Asthenia**	NR
Hexvix	84	M	**9 days**	**Cardiac congestive heart failure**	NR
Hexvix	71	M	**108 days**	**Death**	NR
Hexvix	78	M	**95 days**	**Pneumonia**	NR
W L	79	M	**82 days**	**General physical deterioration**	NR
Hexvix	76	M	**32 Days**	**Myocardial infarction**	NR
Hexvix	64	M	**3 Days**	**Transitional cell carcinoma**	NR
W L	76	M	**33 Days**	**Myocardial infarction**	NR

NR = not related

7.3.2 Nonfatal Serious Adverse Events

In Pool "Overall," 98 (7%) of 1,324 Hexvix-cystoscopy patients experienced an SAE that was similar to the proportion of SAEs in patients receiving only WL cystoscopy, 36 (7%) of 499 patients. The most commonly observed SAEs were in the renal and urinary disorders body system (32 patients, 2%), which is consistent with disease-related complications often experienced by patients with bladder cancer. The proportion of SAEs observed in this body system was similar among all safety data sets: Pool "304/305" Hexvix (15 patients, 3%), Pool "304/305" White Light (14 patients, 3%), and earlier Hexvix studies (Pool "Total") (17 patients, 2%). Hematuria and urinary retention were the most common serious renal and urinary complications, occurring in 11 (1%) patients each for "Overall" Hexvix studies, or 5 (1%) and 7 (1%) patients in Pool "304/305" Hexvix, 6 (1%) and 4 (1%) patients in Pool "Total," compared with 6 (1%) and

3 (1%) patients receiving only WL cystoscopy. Most occurrences of hematuria and urinary retention resolved before the patient completed study participation.

Other SAEs occurring in more than 2 (0.2%) of the 1,324 patients instilled with Hexvix in the six controlled clinical studies included the following: atrial fibrillation (4 patients, 0.3%), benign prostatic hyperplasia (3 patients, 0.2%), chest pain (3 patients, 0.2%), sepsis (3 patients, 0.2%), urinary tract infection (3 patients, 0.3%), hyponatremia (3 patients, 0.2%), transitional cell carcinoma (3 patients, 0.2%), and ureteric cancer (3 patients, 0.2%). Although instances of bladder cancer were reported as an SAE, these events were not considered an AE per the study protocol and represent a misunderstanding by the investigator regarding the definition of AEs.

No SAEs were considered definitely related to Hexvix in any clinical study; however, 11 SAEs observed in 8 patients were of an uncertain relationship. Ten of these SAEs with uncertain relation (7 patients) were observed in earlier Hexvix studies and include sepsis and lung disorder, sepsis, chest pain and tachycardia, urinary retention, hematuria and pyrexia (two instances). The other SAE having an uncertain relationship occurred in pivotal Study 305 in a patient that had mild bladder spasms that lasted for 2 days and resolved without treatment.

Table 40 summarizes the organ classes for the SAEs observed within Study 305 and **Table 41** summarizes the patients with the most frequent SAEs within Study 305. Both of these tables confirm the similarity of the frequency for these SAEs among both the Hexvix treated patients and those only exposed to white light cystoscopy. **Table 42** lists the most frequently occurring SAEs within the overall Hexvix Safety Set of 1,324 patients. None of the SAEs were considered to be related to the administration of Hexvix.

Table 40 : Summary of SAEs Study 305 (Safety Set)

System Organ Class MedDRA preferred Term	Hexvix Group n=421		WL Group n=381	
Total number of SAEs	51		39	
Number Patients with ≥1 SAE	39	9%	32	8%
Renal and urinary disorders	9	2%	12	3%
Cardiac disorders	8	2%	8	2%
Infections and infestations	4	1%	1	<1%
Neoplasms	4	1%	1	<1%
Reproductive	3	1%	1	<1%
Respiratory, thoracic, mediastinal	2	1%	0	0
Surgical & medical procedures	3	1%	3	1%
Injury, procedural complications	2	1%	2	1%
Musculoskeletal, connective tissue	2	1%	1	<1%
Psychiatric disorders	2	1%	0	0
Vascular disorders	2	1%	1	<1%

Table 41 : Most Frequent SAEs Study 305 (Safety Set)

	Hexvix Group N = 421		WL Group N = 381	
Patients with SAEs/Total SAEs	**n=39**	**N = 51**	**n=32**	**N = 39**
Renal & urinary disorders	**9**	**2 %**	**12**	**3 %**
Hematuria	**5**	**1**	**4**	**1**
Urinary perforation	**2**	**1**	**4**	**1**
Bladder perforation	**0**	**1**	**1**	**<1**
Bladder tamponade	**0**	**0**	**2**	**1**
Urinary bladder hemorrhage	**0**	**0**	**1**	**<1**
Bladder spasm	**1**	**<1**	**0**	**0**
Hemorrhage urinary tract	**1**	**<1**	**0**	**0**
Hydronephrosis	**1**	**<1**	**1**	**<1**
Cardiac disorders	**8**	**2 %**	**8**	**2 %**
Atrial fibrillation	**2**	**1**	**1**	**<1**
Cardiac failure congestive	**2**	**1**	**0**	**0**
Myocardial infarction	**2**	**1**	**3**	**1**
Coronary artery disease	**0**	**0**	**1**	**<1**
Angina pectoris	**1**	**<1**	**3**	**1**
Nodal arrhythmia	**1**	**<1**	**0**	**0**

Table 42 : Summary of SAEs Trials 305, 304, 303, 302, 301, 201 (Safety Set)

MedDRA Preferred Term	Hexvix N = 1,324 Overall			
	Related	Uncertain	Not related	Sum +
Total number of SAEs	**0**	**10**	**110**	**120**
Patients with at least 1 SAE	**0**	**8**	**90**	**98**
Tachycardia	0	1	0	1
Chest pain	0	1	2	3
Sepsis	0	2	1	3
Pyrexia	0	1	1	2
Bladder spasms	0	1	0	1
Hematuria	0	1	10	11
Urinary retention	0	2	9	11
Lung disorder	0	1	0	1

+ List incomplete (only most frequent SAEs included)

7.3.3 Dropouts and/or Discontinuations

Overall, 12 (1%) Hexvix-cystoscopy patients enrolled in controlled Hexvix clinical studies were discontinued from the study early because of an AE (**Table 43**). These SAEs included: atrial fibrillation, tachycardia, chest pain, malignant hypertension, death from “natural causes,” urinary bladder excision, pneumonia (n = 2), myocardial infarction, azotemia, esophageal carcinoma, urethral perforation and cardiac death. Only two of the SAEs that led to discontinuation were considered to be related (relationship uncertain) to Hexvix exposure; these were tachycardia and chest pain in one patient.

Table 43 : Summary of AEs Leading to Discontinuation – Overall Safety Set

MedDRA Preferred Term	Hexvix N = 1,324 Overall			
	Related	Uncertain	Not related	Sum
Total number of AEs	0	2	10	12
Patients with ≥ 1 AE	0	1	10	11 (1%)
Cardiac arrhythmia	0	1	1	2
Pneumonia	0	0	2	2
Death	0	0	2	2
Chest pain	0	1	0	1
Azotemia *	0	0	1	1
Urethral perforation	0	0	1	1
Esophageal cancer	0	0	1	1
Urinary bladder excision	0	0	1	1
Malignant hypertension	0	0	1	1

* History chronic nephropathy and bilateral renal cysts [Died – cause not reported]

7.3.4 Significant Adverse Events

Overall, the adverse event pattern following Hexvix administration is indistinguishable from the pattern observed during and following routine cystoscopy. Isolated SAEs reported during the Hexvix postmarketing surveillance included cases of anaphylactic shock, vascular purpura with cutaneous necrosis and pruritis. Thus, Hexvix may have a risk of hypersensitivity reactions and/or anaphylaxis.

The most frequent adverse events following Hexvix instillation and blue light cycstoscopy relate to renal impairment. **Table 44** lists 17 examples of renal impairment occurring post Hexvix instillation and blue light cystoscopy, and all were determined to not be related to the study product.

Table 44 : **Renal Impairment AEs - Safety Set – All Non-Related**

	Cases	Severity			Outcome
		Mild	Moderate	Severe	
Renal failure *	2			2	Resolved
Azotemia ~	1			1	Death
Urine output decreased	7	5	2		Resolved
Creatinine increased	3	2	1		Continuing
Creatinine increased	2	2			Resolved
BUN increased	1	1			Continuing
Hyperuicemia	1	1			Resolved

* 30 Days & 84 Days post procedure

~ 233 days post procedure

7.4.1 Common Adverse Events

The following list of adverse events and their frequencies reported in the overall safety data base are the same adverse events and their frequency associated with standard cystoscopy and trans urethral resection of the bladder (TURB).

Hematuria – 15.8%
Procedural pain – 9.2%
Dysuria -8.5%
Bladder spasm – 6.0%
Urinary retention – 5.3%
Nausea – 5%
Bladder pain – 3.8%
Urinary tract infection – 3.8%
Frequency 3.5%
Abdominal pain 2.9%
Headache – 2.6%

7.4.2 Laboratory Findings

Summary of Laboratory AEs

The majority of systemic AEs resulting from laboratory changes were consistent with complications associated with cystoscopy. There was no indication that Hexvix adversely affected clinical hematology and serum chemistry parameters.

Table 45 : Summary of Laboratory AEs

MedDRA Preferred Term	Hexvix N = 1,324 Overall							
	Mild		Moderate		Severe		Total	
	R	N R	R	N R	R	N R	R	N R
Total number of AEs	12	34	2	12	0	8	14	54
Patients with ≥ 1 AE	11	25	2	10	0	6	13	41 (3%)
Anemia	1	3	1	3	0	2	2	8
Leucocytosis	7	2	0	0	0	0	7	2
Renal impairment *	0	4	0	1	0	1	0	6
Bilirubin ↑	3	0	0	0	0	0	3	0
Calcium ↓	0	3	0	0	0	0	0	3
Glucose ↑	0	3	0	0	0	0	0	3
Glucose ↓	0	1	0	0	0	0	0	1
Potassium ↓	0	5	0	2	0	0	0	7
Potassium ↑	0	0	0	1	0	0	0	1
Sodium ↓	0	3	0	2	0	1	0	6
Oxygen saturation ↓	0	2	0	0	0	0	0	2

NR = not related

* Azotemia, urinary retention, elevated creatinine or elevated BUN

7.4.3 Vital Signs

In general, data provided no indication that Hexvix adversely affected vital signs and physical examination findings.

7.4.4 Electrocardiograms (ECGs)

Whereas this product is not administered systemically, electrocardiograms were not evaluated during the development program.

7.4.6 Immunogenicity

Immunogenicity studies were not performed during the development program.

7.5 Other Safety Explorations

For this topically administered, single administration use diagnostic agent, no formal drug-drug, drug-food, or drug-disease interaction studies were conducted as part of the development program, and no interactions were analyzed in any of the studies conducted with Hexvix.

7.5.1 Dose Dependency for Adverse Events

See Section 7.2.2

7.5.2 Time Dependency for Adverse Events

See Section 7.2.1

7.5.4 Drug-Disease Interactions

Based on the generally aged population participating in the Phase 2 and Phase 3 studies and the indication of Hexvix cystoscopy, patients with multiple concomitant medications and disease states were enrolled. No apparent drug-drug or drug-disease interactions were observed with Hexvix administration. Based on the limited systemic uptake of Hexvix and the instability in human blood, any potentially interfering pharmacokinetic interactions with other drugs would not be predicted. Drugs likely to be concomitantly administered with Hexvix in the clinical setting of cystoscopy and resection may include the same local anesthetics (i.e., lidocaine and bupivacaine hydrochloride with or without epinephrine) or general anesthetics (i.e., fentanyl, propofol, and sufentanil) as used in the clinical trials.

7.5.5 Drug-Drug Interactions

For this topically administered, single administration use diagnostic agent, no formal drug-drug, drug-food, or drug-disease interaction studies were conducted as part of the development program, and no interactions were analyzed in any of the studies conducted with Hexvix.

7.6 Additional Safety Evaluations

Pending completion of Review Cycle.

7.6.1 Human Carcinogenicity

Pending ongoing review by Pharm/Tox

7.6.2 Human Reproduction and Pregnancy Data

Pending ongoing review by Pharm/Tox

7.6.3 Pediatrics and Assessment of Effects on Growth

The Hexvix (hexylaminolevulinate HCl) full waiver was reviewed by the PeRC PREA Subcommittee on October 14, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable because the disease/condition does not exist in children. The PeRC agreed with the Division to grant a full pediatric waiver for this product.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

For this topically administered, single administration use diagnostic agent, no potential for drug abuse would be anticipated with Hexvix.

7.7 Additional Submissions / Safety Issues

The proposed proprietary name Hexvix has been determined to be vulnerable to name confusion that could lead to medication errors (b) (4) Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has objected to the proprietary name, Hexvix, for this product and have concluded that the name is unacceptable (b) (4)

(b) (4)

It was recommended to the sponsor that they submit a new request for a proposed proprietary name review.

8 Postmarket Experience

Postmarketing Safety Experience

During the period of 17 January 2009 (cut-off date for NDA 22-555) through 30 September 2009, marketing approval for the same indication was obtained in one additional country, Korea (total of 29 countries). During that same interval, more than (b) (4) patients have received Hexvix in combination with a Karl Storz PDD system in Europe for a total of 57,000 patients exposed to Hexvix to date (sales as of 30 September 2009); of these (b) (4) patients, at least (b) (4) patients have received Hexvix in combination with a Karl Storz D-Light C PDD system. During the Hexvix postmarketing surveillance period through September 2009, isolated SAEs of anaphylactic shock, vascular purpura with cutaneous necrosis and pruritis have been reported among patients exposed to Hexvix. Thus, Hexvix may have a risk of hypersensitivity reactions and/or anaphylaxis. (Case summaries below/all recovered/all confounded by concomitant peri-operative medications).

Overall, the adverse event pattern following Hexvix administration is indistinguishable from the pattern observed during routine cystoscopy except for the possibility of an increased risk for anaphylaxis/hypersensitivity.

Brief Summaries of 3 Cases of Possible Anaphylaxis/Hypersensitivity

Case #1 Hypotension, Atrial fibrillation, Urticaria & Swelling in Throat
69 year old man underwent Hexvix instillation (3 hours), negative cystoscopic exam and TURP (under spinal anesthesia) which was associated with profuse bleeding (800cc) that prompted termination of the surgery; patient was noted to also have urticaria, swelling in throat (sensation), chest pressure, hypotension, atrial fibrillation, loss of consciousness. Serum tryptase was elevated immediately post-procedure and a follow-up skin prick test with undiluted Hexvix was reported as "positive" for Hexvix sensitivity.

Case #2 Hypotension, Bradycardia, Urticaria & ECG Evidence of Ischemia
84 year old man underwent Hexvix Cysto for hematuria - duration about 2 hours; 45 minutes after the procedure developed urticaria (perineum, abdomen, back and down legs) hypotension, bradycardia and ECG Ischemia (first degree heart block & T-wave inversion).

Case #3 Vascular Purpura & Skin Necrosis
68 year old man underwent Hexvix Cystoscopy and 10 days later developed vascular purpura with skin necrosis lower limbs; Negative tests for cryoglobulin, autoimmune assessment, anticytoplasmic antibodies, and serology. Association with Hexvix "unclear."

(b) (4)

Appendices

9.1 Literature Review/References

Review of published literature added little to the material included with this submission.

9.2 Labeling Recommendations

Due to the compressed timeline associated with this priority review and the necessity for completion of this review prior to the labeling review, current labeling recommendations are incomplete. Several important outstanding labeling issues have been referred to in this document and include:

- When lesions are detected by blue light cystoscopy alone, the false-positive detection rate is slightly higher than when detected by white light cystoscopy alone.

- Biopsy/resection with white light cystoscopy prior to blue light cystoscopy, inflammation and instillation of BCG or chemotherapy have the potential to increase the false-positive detection rate.

- Performance of blue light cystoscopy without white light cystoscopy should not be done as it will result in the missing of pathologic lesions.

- Hexvix may have the potential of causing hypersensitivity reactions and rarely anaphylaxis.

- The safety of repeated instillation of Hexvix and repeated exposure to blue light cystoscopy on bladder epithelial cells has not been fully evaluated.

9.3 Advisory Committee Meeting

FDA is convening an advisory committee to discuss the clinical data within this New Drug Application (NDA) for Hexvix® for use in the cystoscopic detection of non-muscular invasive papillary cancer of the bladder. The main goal of this advisory committee will be to obtain the committee's perspective regarding the efficacy and safety data as presented by the company and summarized by the FDA, in the context of FDA's preliminary concerns. Due to the timeline associated with a priority review as in this case, this clinical review is being completed prior to the projected date of the advisory committee.

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

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/s/

SCHELDON KRESS
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