Clinical Study Protocol

Study Title: A prospective, comparative within patient controlled, multi-center study of Hexvix blue light cystoscopy and white light cystoscopy in the detection of bladder cancer

Study Number： **YHCT-HEX-B1**

Version： **V 2.2**

Date： **Feb 6th, 2023**

Sponsor: **Photocure ASA**

China Registration Agent： **Jiangsu Yahong Meditech Co., Ltd.**

Confidentiality Statement
All information contained within this study protocol is the property of the sponsor and is therefore only for review by the investigators, co-investigators, Ethics Committee, regulatory authorities and other relevant medical institutions. Without a prior written permission of the sponsor, except during signing an informed consent form with subjects and offering necessary explanations, disclosure of any information to a third party unrelated to the present trial is strictly prohibited.

Protocol Signature Page

(Sponsor)

I agree that:

- In strict accordance with the protocol, the current ICH *Good Clinical Practice for drug Clinical trials* (GCP) and the National Medical Products Administration (NMPA) GCP guidelines as well as applicable regulations and guidelines for conducting the study.
- Be responsible for initiating, applying for, organizing and funding this clinical trial, and implementing the audit of the clinical trial.

I have already read the clinical trial protocol entirely, and I fully agree all the provisions listed in the protocol.

Sponsor: Photocure ASA

Signature: **Date:**

Protocol Signature Page

(Principal Investigator)

I agree that:

- This clinical trial shall be conducted in strict accordance with the protocol, current ICH GCP and NMPA GCP guidelines, and applicable regulations and guidelines.
- All information provided by the sponsor shall be maintained in accordance with the confidentiality requirements and shall be marked as confidential when submitted to the Independent Ethics Committee (IEC).

I have already read the clinical trial protocol entirely, and I fully agree all the provisions listed in the protocol.

Clinical trial institution: Peking Union Medical College Hospital

Principal Investigator: Professor Hanzhong Li

Signature: **Date:**

Protocol Signature Page

(Statistician)

I agree that:

- The statistical analysis of this clinical trial shall be carried out in strict accordance with the protocol, current ICH GCP and NMPA GCP guidelines, and applicable regulations and guidelines.
- Keep all information of sponsor in accordance with confidentiality requirement.

I have already read the clinical trial protocol entirely, and I fully agree all the provisions listed in the protocol.

Statistical institution:

Statistician:

Signature: **Date:**

Protocol Signature Page (Sub-centers)

Protocol No.	YHCT-HEX-B1	**Version and date**	V2.2 / Feb 6th, 2023
Study title	A prospective, comparative, within patient controlled, multi-center study of Hexvix blue light cystoscopy and white light cystoscopy in the detection of bladder cancer		
Study center No.		**Investigator:**	
Study center			

I have already read the clinical trial protocol entirely, and and understand its requirements. I agree to follow the protocol and schedule for the clinical trial. Any modification that is not approved by the sponsor and/or CRO and IEC is considered to be a protocol violation.

I agree to conduct the trial in accordance with the current ICH GCP and NMPA GCP guidelines and applicable regulations and guidelines, and to accept the monitoring / audit of the clinical trial by the sponsor and/or CRO and the verification/inspection by the drug regulatory authorities.

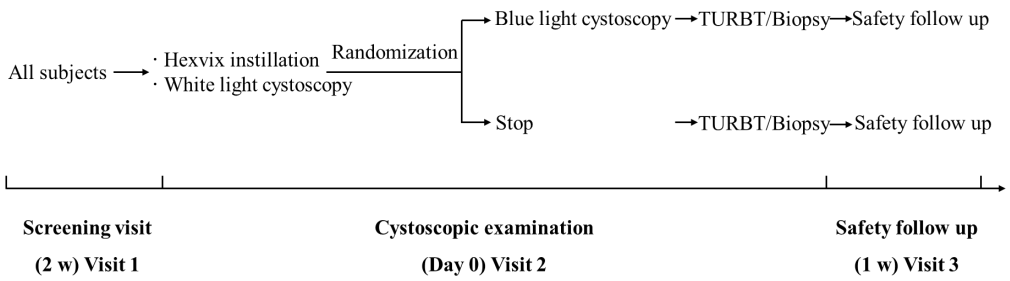
I agree to use only the trial supplies specified in the protocol including investigational drugs.

Principal Investigator signature

Name	Date	Signature

PROTOCOL SYNOPOSIS

Study Number	YHCT-HEX-B1
Study Title	A prospective, comparative, within patient controlled, multi-center study of Hexvix blue light cystoscopy and white light cystoscopy in the detection of bladder cancer
Version	V 2.2
Date	Feb 6th, 2023
Sponsor	Photocure ASA
China Registration Agent	Jiangsu Yahong Meditech Co., Ltd.
Clinical Phase	Phase 3
Objective	**Primary Objective:** • To compare Hexvix blue light cystoscopy with white light cystoscopy in the detection of bladder cancer. **Secondary Objectives:** • Comparison of detection of patients with CIS lesions by Hexvix blue light cystoscopy and white light cystoscopy. • Comparison of detection rates of bladder lesions of Hexvix blue light cystoscopy and white light cystoscopy per lesion type (PUNLMP, CIS, Ta, T1, T2-4). • Comparison of the proportion of false positive lesions detected with Hexvix blue light cystoscopy and white light cystoscopy. • Evaluation of the safety of Hexvix in patients with bladder cancer.
Study Design	A prospective, comparative, within patient controlled, multi-center study of Hexvix blue light cystoscopy and white light cystoscopy in the detection of bladder cancer. Approximately 380 patients with suspected or confirmed bladder cancer will be enrolled until a total of 94 patients with pathological confirmed Ta, T1 or CIS are included. There will be a maximum of three regular study visits: A screening visit (-2 weeks), a cystoscopy examination (Day 0), and the safety follow-up period (1 week±3 days), in which the screeing visit and cystoscopy examination could be conducted in the same visit.



Study design

At the start of the study, a minimum of four subjects included at each center will be training subjects. These subjects will receive the Hexvix administration and undergo white and blue light cystoscopy with tumor resection as below. They will receive the same safety follow up as all the other included patients, after completing the safety follow-up for 1 week, the subjects will be treated according to hospital's clinical routine by the investigator. These patients are not part of the efficacy analyses.

To reduce possible bias in assessment of the objectives, a small number of subjects will be randomized to not continue with Hexvix blue light cystoscopy following white light cystoscopy.

Consented, eligible subjects (Visit 1) will be instilled with 50 mL Hexvix 8 mM solution for one hour (Visit 2). After bladder evacuation, the following procedure will be utilized to accomplish the cystoscopic examination of each subject：

1. Turn on the white light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under white light, record lesion number, size and location.
2. Randomization:
    a) If the patient is not randomized to undergo blue light mapping, proceed to step 3.
    b) If the patient is randomized to continue with blue light mapping, or subjects for investigator training procedure, then they will undergo blue light cystoscopy. Turn to the blue light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under blue light, record lesion number, size and location.
3. All papillary lesions detected will be resected using Transurethral Resection of the Bladder Tumor (TURBT) and all flat and suspicious lesions detected will be biopsied. The lesions resected and biopsied should be marked and pathologically examined seperately. For patients randomized to undergo blue light cystoscopy and for training patients,

	the completeness of the resection should always be checked under blue light before finalizing the TURBT procedure until it is ensured that all lesions and suspicious areas are completely resected. Both biopsied and resected tissue will be examined by the local pathologist, then evaluated by independent and blinded central pathologists. Central pathology results will be used as reference standard in the study efficacy endpoints. All subjects (including the training patients) will receive a safety follow-up at day 7 (visit 3) after day 0 cystoscopy (visit 2), after completing the safety follow-up for 1 week, the patients will be treated according to hospital routines by investigator.
Number of Patients	Approximately 380 patients are planned to be included in the study, to ensure 94 patients with pathological confirmed bladder cancer (Ta, T1 and CIS).
Number of Centers	About 5-10 centers in China
Study Duration	The duration of each patient's participation in the study is about 3 weeks (including a 2-week screening period, a day 0 test period, and a 1-week safety follow-up period)
Patients	**Inclusion Criteria：** 1. Volunteer to participate in the study; fully understand with signing of informed consent; willing to follow and have the ability to complete all experimental procedures. 2. Suspicious or confirmed patients with bladder cancer. 3. Age 18 or older. **Exclusion Criteria：** 1. Gross haematuria. (Note: Gross haematuria is defined as a heavy bladder bleed resulting in marked amounts of blood in the urine, which may visually limit cystoscopy. Where the haematuria is light, the patient should not be excluded, if in the investigator's opinion, rinsing and/or electro-cautery during cystoscopy will alleviate the possible interference with cystoscopy). 2. Patients who received BCG immunotherapy or intravesical chemotherapy within 6 weeks prior to the procedure. 3. Porphyria. 4. Known allergy to hexaminolevulinate hydrochloride or a similar compound. 5. Pregnancy or breast feeding or patients of child-bearing potential, including men with partners of child-bearing potential, who are unwilling to take barrier contraceptives from 2 weeks before medication to 28 days

	after the medication. (Note: Child-bearing potential is defined as women who are ovulating, pre-menopausal or not surgically sterilized. All women of child-bearing potential must document a negative pregnancy test before study inclusion and use adequate contraception during the study). 6. Participation in other clinical studies with investigational drugs/investigational device either concurrently or within the last 30 days prior to the first study cystoscopy. 7. Patient who is the investigator or any sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol. 8. Patients that the investigator believed were unlikely to comply with the protocol. 9. Subjects with contraindications to white light cystoscopy.
Drug / Device	**Drug name:** Hexvix (hexaminolevulinate hydrochloride, for intravesical solution, for bladder instillation only) as the photosensitizer to use with blue light cystoscopy **Active ingredient:** Hexaminolevulinate hydrochloride **Device:** Cystoscopic equipment with necessary filters to allow both standard white light cystoscopy and blue light (wavelength 380–450 nm) fluorescence cystoscopy
Comparative Drug	Not applicable
Efficacy Endpoint	**Primary Efficacy Endpoint：** • The proportion of patients with histology-confirmed tumors (Ta, T1, or CIS) who have at least one such tumor found by Hexvix but not by white light cystoscopy. **Secondary Efficacy Endpoint：** • The proportion of patients with one or more CIS lesions detected only by Hexvix blue light cystoscopy not by white light cystoscopy. • The lesion detection rate for Hexvix blue light cystoscopy compared to white light cystoscopy per lesion type (PUNLMP, CIS, Ta, T1, T2-4). • The proportion of false positive lesions detected with Hexvix blue light cystoscopy and white light cystoscopy.
Safety Endpoint	The proportion of patients with AEs during the study.

Statistics	**Sample Size:** Sample size calculation for the primary efficacy analysis is based on an exact test for a single proportion. Statistical assumption is based on primary endpoint that P (null hypothesis) is 10%, P (alternative hypothesis) is 20% and a power of 80%, α (1-side) is 0.025, a total of 94 patients with histologically confirmed Ta, T1, and CIS stage bladder cancer are needed. Assuming that 35% of subjects will have bladder cancer after Hexvix-assisted blue light cystoscopy and/or white light cystoscopy, bladder cancer with Ta, T1 and CIS stage accounting for 75%, 359 subjects are expected to be enrolled in this trial. Considering the 5% drop-out rate, a total of about 380 subjects are required. The study will continue until 94 subjects have bladder cancer after Hexvix-assisted blue light cystoscopy and/or white light cystoscopy and are pathologically confirmed as Ta, T1, and CIS stage bladder cancer. Note: A minimum of 4 subjects included at each center will be training subjects, and those training subjects are in addition to the estimated sample size. Moreover, training subjects are not included in the randomization procedure and efficacy endpoints analysis, but included in the safety analysis. **Statistical Analysis Method:** **Efficacy:** Efficacy endpoint analysis will be based on full analysis set (FAS) / modified full analysis set (mFAS) and per protocol set (PPS) / modified per protocol set (mPPS). Primary efficacy endpoint will be analyzed based on subjects who received Hexvix instillation and continue with blue light cystoscopy, and are pathologically confirmed as Ta, T1, and CIS stage bladder cancer, training patients will not be included. For analysis of the primary efficacy endpoint (The proportion of patients with histology-confirmed tumors (Ta, T1, or CIS) who have at least one such tumor found by Hexvix but not by white light cystoscopy), an exact test for single proportion, using the cumulative binominal distribution, with a significance level of 0.025 (1-sided) will be used, based on the mFAS and mPPS, and the 95% confidence interval for the detection rate will be calculated. Secondary efficacy endpoints will be analyzed descriptively, including event rate and 95% confidence intervals based on the FAS and PPS. Exact 95% confidence interval will be calculated similarly to that of the primary efficacy endpoint. But no formal statsitical inference will be made to the secondary efficacy endpoints. If the establishment of confidence intervals is based on biopsy/TURBT data, Bladder biopsy/TURBT data should be assumed to be independent of each other. Efficacy data will be tabulated in detail. **Safety:** Safety analysis will be based on safety set. The reported adverse events (including local reactions) will be coded according to MedDRA terminology. The events will be tabulated by System Organ Class and by Preferred term.

	Adverse events will also be tabulated versus severity and relation to treatment. Physical examination and vital signs at each visit will be presented using descriptive statistics. **Interim Analysis:** No interim analysis is planned for this study.

Study Flow Chart

Visit Number	**Visit 1**	**Visit 2[9]**	**Visit 3[10]**
Visit Type	**Screening**	**Detection**	**Safety follow-up**
Visit (D)	**2 weeks（D-14~D0）**	**D0**	**1 week（D7±3）**
Informed consent [1]	√		
Demography [2], Medical history, and Surgery history [3]	√		
Medication history	√		
Inclusion/exclusion	√		
Vital signs [4]	√	√	√ [12]
Physical exam [5]	√	√	
Pregnancy test [6]	√	√	
Randomization [7]		√	
Assessment of bladder symptoms		√	
Cytology		√	
Hexvix administration（bladder instillation）		√	
White light, or white light and blue light cystoscopy		√	
Lesion assessment/mapping		√	
Biopsies/TURBT histology		√ [11]	
Complications, Adverse events [8]	√	√	√
Concomitant medications/procedures	√	√	√

1. Before any study related procedures are performed, patient must then sign and date the informed consent form.
2. Demographic information includes: gender, age, ethnicity, height, weight, body mass index, and history of allergies, drug abuse, smoking, alcohol abuse, and blood donation.
3. All bladder cancer-related medical history and surgical history should be recorded in detail and distinguished from other diseases without the time limitation. Other medical history and surgical history within the past 2 years should be recorded.
4. Vital signs include: body temperature, sitting blood pressure, heart rate, and breathing rate. Vital signs should be measured when the investigator judges that the subject's condition is stable.
   Note: Vital signs should be examined before and after surgery on Visit 2.
5. According to organs and systems, a comprehensive physical examination includes: general conditions, head and neck, lymph nodes, skin, chest, abdomen, musculoskeletal system (including limbs and spine) and nervous system. If the subject has already undergone the examination within 7 days before the administration, visit 2 can no longer perform the examination.
6. Pregnancy test (only for women of childbearing age): The pregnancy test for women of childbearing age during the screening period must be negative. If the subject has undergone a pregnancy test within 7 days

before the administration, visit 2 can no longer perform the test. During the study period, urine pregnancy test can be performed as needed. If the urine pregnancy result is positive, a serum pregnancy test is required to confirm. If it is confirmed positive, the subject needs to withdraw from the test, and the investigator will continue to follow up the subject until the end of the pregnancy.

7. To reduce possible bias in the white light cystoscopy (the comparator standard is white light cystoscopy in the study design), randomization will be done: a) The subjects randomized to not continue with Hexvix cystoscopy will receive TURBT and safety follow-up after 1week and routine clinical practice by the investigator. b) The subjects randomized to continue with Hexvix cystoscopy or for training purpose of the investigator, will undergo Hexvix cystoscopy, TURBT and later process.
8. All adverse events that occurred between ICF signed and the last visit, regardless of their severity and relationship with the study drug, should be recorded. New adverse events occurred from ICF to drug administration or worsened AEs should be recorded and reported as adverse events/serious adverse events.
9. Visit 2 should be conducted within 14 days after the end of Visit 1, and can be combined with Visit 1.
10. Visit 3 can be conducted by telephone visit, if AEs are identified during the follow-up, the investigator should evaluate whether subjects need to return to the investigational site according to their conditions.
11. Visit 2 is for cystoscopy and pathological tissue resection/biopsy sampling. Actual clinical finishing time shall be recorded as record time points for histopathological evaluation results.
12. The vital signs in Visit 3 are optional and needs to be taken only in case the subject comes into the hospital.

TABLE OF CONTENT

List of Abbreviations and Definitions of Terms

Abbreviation	Full name in English	Full name in Chinese
AE	Adverse event	不良事件
BCG	Bacillus calmette guerin	卡介苗
BL	Blue light	蓝光
CTCAE	Common terminology criteria for adverse events	不良事件通用术语标准
CIS	Carcinoma in situ	原位癌
CRA	Clinical research associate	临床监察员
CRF	Case report form	病历报告表
CRO	Contract research organization	合同研究组织
DM	Data management	数据管理
DVP	Data verification plan	数据核查计划
eCRF	Electronic case report form	电子病历报告表
EDC	Electronic data capture	电子数据采集系统
FDA	Food and drug administration	美国食品药品监督管理局
GCP	Good clinical practice	药物临床试验质量管理规范
HAL	Hexaminolevulinate	5-氨基酮戊酸己酯
IEC	Independent ethics committee	独立的伦理委员会
IRB	Institutional review board	机构审查委员会
ITT	Intention to treat	意向治疗
MedDRA	Medical dictionary for regulatory activities	ICH 国际医学用语词典
mFAS	modified full analysis set	调整的全分析集
mPPS	modified per protocol set	调整的符合方案集
NCI	National cancer institute	国立癌症研究所

Abbreviation	Full name in English	Full name in Chinese
NMIBC	Non-muscle invasive bladder cancer	非肌层浸润性膀胱癌
NMPA	National medical products administration	国家药品监督管理局
PAP	Photoactive porphyrines	光敏卟啉
PP	Per protocol	符合方案
PT	Prefered term	首选术语
PUNLMP	Papillary urothelial neoplasm of low malignant potential	低度恶性潜能乳头状尿路上皮肿瘤
QA	Quality assurance	质量保证
SAE	Serious adverse event	严重不良事件
SOC	Systematic organ classification	系统器官分类
SUSAR	Suspected unexpected serious adverse reaction	可疑且非预期严重不良反应
TURBT	Transurethral resection of the bladder tumor	经尿道膀胱肿瘤电切术
WHO DD	World health organization drug dictionary	世界卫生组织药物词典
WL	White light	白光

1. Introduction and Study Rationale

1.1 Disease Introduction

In the Western world, bladder cancer is the fourth most common malignancy in men and the eighth most common in women. An estimated 80,470 new cases of urinary bladder cancer (61,700 men and 18,770 women) be diagnosed in the United States in 2019 with approximately 17,670 deaths (12,870 men and 4,800 women) occurring during this same period. [1]. In China, bladder cancer is the eighth most common in malignant cancer, and the sixth most common in men [2]. Although the incidence of bladder cancer in China is about half of Western countries, " Morbidity and Mortality data in Cancer Registry Area of China" released from 2009 to 2012 shows that the incidence of bladder cancer has steadily increased from 6.41 per 100,000 to 7.49 per 100,000, with a compound annual growth rate of 5.3%, from 2005 to 2008.

Over ninety percent of bladder tumors are urothelial cell carcinoma, usually papillary and multi centric, while squamous cell carcinoma accounts for 5% and adenocarcinoma accounts for 2% [3,4]. In patients with the diagnosis of bladder cancer, about 70% present initially as non-muscle invasive bladder cancer (NMIBC), and the remainder as muscle invasive cancer. Among the NMIBC, approximately 70% are present as Ta lesions, 20% as T1, and approximately 10% as carcinoma in situ (CIS or Tis) [5].

Diagnosis of bladder cancer is mainly confirmed by a combination of cystoscopic examination, biopsy and urine cytology [6,7]. NMIBC is treated by transurethral resection of the bladder (TURBT) to remove the tumor and allow for pathologic analysis of the biopsied specimen, establishing the diagnosis and providing important information about the tumor grade and depth of bladder invasion.

Recurrence of bladder tumors is common, and may be caused by residual tumor after incomplete resection, microsatellites missed during initial TURBT or true recurrence [8,9,10]. Depending on a patient’s characteristics, after transurethral resection the probability of recurrence at one-year ranges from about 15% to 61% and from 31% to 78% at 5 years. The major prognostic factors for recurrence and progression are presence of CIS, tumor multiplicity, size, previous recurrence rates, tumor stage and tumor grade [11].

White light (WL) cystoscopy has been the major technique for detecting primary and recurrent bladder carcinomas. While papillary tumors usually can be detected with white light cystoscopy, flat lesions such as CIS may be more difficult to detect under these conditions. However, techniques based on photoactive porphyrins, such as hexaminolevulinate (HAL), that accumulate preferentially in neoplastic tissue, have been developed to improve detection of non-muscle invasive bladder lesions. Under blue light (BL) exposure tumor lesions emit red light and can easily be detected with a cystoscope.

1.2 Drug Introduction

Hexaminolevulinate hydrochloride is approved in Europe under the brand name Hexvix for the following indication: “Hexvix blue light fluorescence cystoscopy is indicated as adjunct to standard white light cystoscopy to contribute to the diagnosis and management of bladder cancer in patients with known or high suspicion of bladder cancer”. In the United States the product is approved under the brand name Cysview for the following indication: Cysview is an optical imaging agent indicated

for use in the cystoscopic detection of carcinoma of the bladder, including carcinoma in situ (CIS), among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy, or in patients undergoing surveillance cystoscopy for carcinoma of the bladder.

1.2.1 Nonclinical Study

Hexaminolevulinate (HAL) hydrochloride (HCl) is the drug substance of Hexvix. Hexvix has been globally approved for use in diagnosis of bladder cancer following intravesical administration. Hence, a complete package of nonclinical pharmacology and toxicology documentation exists for this indication. For use of HAL HCl in other indications in development, additional studies have been performed to investigate reproductive and developmental toxicology and local tolerance data after cervical application. The toxicology program performed for HAL has included safety pharmacology and assessments of systemic toxicity that might be due to systemic absorption after local administration. In addition, the potential for systemic toxicity of HAL has been assessed after single-dose (mice and rats) and repeat-dose (rats and dogs) intravenous administration. An extensive package of genotoxicity studies and a reproduction toxicity program has been completed. The combination of HAL and light has also been investigated in both local tolerance and genotoxicity studies. With the completed nonclinical studies, the safety of HAL is considered adequately documented. More information is available in the investigator brochure.

1.2.2 Clinical Study

Belowing are brief presentation of Hexvix clinical studies, more information is available in the investigator brochure [12].

Blue light cystoscopy with Hexvix offers considerable benefits over white light cystoscopy in the detection of NMIBC. This has been supported by a number of clinical phase III trials [13,14,15], which have demonstrated that 16-29% of patients had one or more Ta or T1 tumor that were detected by blue light cystoscopy with Hexvix and not by white light cystoscopy. A pivotal phase III study showed that in 16% of the patients with Ta or T1 tumors at least one additional tumor was detected with blue light cystoscopy with Hexvix that was missed with white light cystoscopy (p=0.001) [15]. This phase III study also demonstrated that improved detection of Ta/T1 bladder tumors enables a more complete resection, resulting in a significant reduction of recurrence rates within 9 months. During the surveillance period, for ITT (the Intention-To Treat) analysis 128/271 patients (47%) in the Hexvix group and 157/280 patients (56%) in the white light group had tumor recurrence (p=0.026). The PP (Per Protocol) results were similar to those for the ITT group. The relative reduction in cancer recurrence at 9 months was 16% for the ITT analysis and 21% for the PP analysis. There was a trend that more patients in the group treated with white light only experienced recurrence of higher stage tumors (T1 or CIS) compared to patients treated with blue light cystoscopy with Hexvix.

Results from three phase III studies demonstrated that blue light cystoscopy with Hexvix improves the detection of CIS lesions significantly, which has consequences for patient management and may improve prognosis [11, 16, 17]. One study included 211 patients with suspicion or known bladder cancer. CIS lesions were found in 39% of evaluable patients and in 22% of these patients CIS lesions were detected only with blue light cystoscopy with Hexvix. Data from the other study showed that 30% of the patients had CIS and among these 16% were detected only by blue light cystoscopy with Hexvix.

In the last study [17], among 26 patients with CIS, 34.6% had CIS detected only with blue light cystoscopy with Hexvix.

Two small single center studies reported improved detection of bladder cancer lesions using blue light cystoscopy with Hexvix [18, 19], and another small single center study documented the use of Hexvix in the early follow up of high-risk patients [20]. The studies were conducted in the OR setting, and concluded that blue light cystoscopy with Hexvix helps to detect evolving CIS and dysplasia which can be considered a precursor of CIS, and plays an important role in preventing disease progression.

The safety of Hexvix instillation into the bladder has been evaluated in all clinical trials, and similar AE profiles have been reported for patients undergoing blue light cystoscopy with Hexvix versus patients treated with white light cystoscopy only [15]. Most AEs were mild to moderate and were expected during bladder examination by cystoscopy, and were considered to be related to general anesthesia, biopsy, tumor resection, cystoscopy or the patients' underlying disease. The conclusions were that Hexvix is well tolerated. A review of safety information from clinical studies and postmarketing data did not reveal additional toxicity during repeated use of Hexvix [21].

The trial is a phase III, prospective, comparative, within patient controlled, multi-center study of Hexvix blue light cystoscopy and white light cystoscopy in the detection of bladder cancer and will be conducted only in China to evaluate the efficacy and safety of Hexvix blue light cystoscopy in Chinese population.

2. Study Objectives

2.1 Primary Objective

- To compare Hexvix blue light cystoscopy with white light cystoscopy in the detection of bladder cancer

2.2 Secondary Objective

- Comparison of detection of patients with CIS lesions by Hexvix blue light cystoscopy and white light cystoscopy.
- Comparison of detection rates of bladder lesions of Hexvix blue light cystoscopy and white light cystoscopy per lesion type (PUNLMP, CIS, Ta, T1, T2-4).
- Comparison of the proportion of false positive lesions detected with Hexvix blue light cystoscopy and white light cystoscopy.
- Evaluation of safety of Hexvix in patients with bladder cancer.

3. Selection and Withdrawal of Subjects

3.1 Inclusion Criteria

The subject must fulfil all the following criteria to be included in the study：

1. Volunteer to participate in clinical study; thoroughly informed, signed and dated the informed consent form; willing to follow and have the ability to complete all trial procedures.
2. Suspicious or confirmed patients with bladder cancer.
3. Age 18 or older.

3.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study：

1. Gross haematuria. (Note: Gross haematuria is defined as a heavy bladder bleed resulting in marked amounts of blood in the urine, which may visually limit cystoscopy. Where the haematuria is light, the patient should not be excluded, if in the investigator's opinion, rinsing and/or electro-cautery during cystoscopy will alleviate the possible interference with cystoscopy).
2. Patients who have received BCG immunotherapy or intravesical chemotherapy within the past 6 weeks prior to the procedure.
3. Porphyria.
4. Known allergy to hexaminolevulinate hydrochloride or a similar compound.
5. Pregnancy or breast feeding or patients of child-bearing potential, including men with partners of child-bearing potential, who are unwilling to take barrier contraceptives from 2 weeks before medication to 28 days after the medication. (Note: Child-bearing potential is defined as females who are ovulating, pre-menopausal or not surgically sterilized. All women of child-bearing potential must document a negative pregnancy test before study inclusion and use adequate contraception during the study).
6. Participation in other clinical studies with investigational drugs/investigational device either concurrently or within the last 30 days prior to the first study cystoscopy.
7. Patient is the investigator or any sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
8. Patients that the investigator assessed unsuitable to the study.
9. Subjects with contraindications to white light cystoscopy.

3.3 Elimination criteria

Data will be submitted to the principal investigator, sponsor and statistical institution during data review meeting to determine if there is any individual case that needs to be eliminated before statistical analysis of the data is performed.

3.4 Withdrawal criteria

1）Investigator's decision to withdraw

Withdrawal from the study refers to the fact that the selected subjects are unsuitable to continue the study during the course of the study, and the investigator decides to withdraw the case from the study. For subjects withdrawn from the study, the investigator should fill in the reason for withdrawal in the electronic case report form (eCRF), complete the evaluation items that can be completed, and fill in the end-of-treatment follow-up record form including the last time of contact. In the following, the criteria for the investigator's decision to withdraw are listed. Beware that this is only applicable before dispensing of the Investigational Drug and Device.

- The investigator believes that continuing treatment will be detrimental to the subject. [such as in the clinical trial, the subject has some comorbidities (documented as medical history), complications or worsening of the condition, and it is not suitable to continue the trial. (Note: this is only applicable to the time frame between Visit 1 and Visit 2. It stays unchanged that comorbidities should be evaluated accordingly before inclusion. Complications or worsening of the condition of the patient (AE) after dispensing of the Investigational Drug and after the procedure should not lead to a withdrawal of the patient, but should stay in the study for the Follow Up of AEs or complications for safety reasons.)]
- Major protocol deviations.
- The subject did not follow the doctor's advice and used other treatments without authorization, which affected the evaluation.
- The subject's poor compliance affects the efficacy and safety assessments.
- Other. (Note: The specific reason should be recorded in the "Specific Description" section of the electronic case report form (eCRF), for example: non-compliance.)

2）Subject's decision to withdraw

Subjects, unwilling to continue to participate in clinical research, have the right to withdraw from the study at any time of the study according to the provisions of the informed consent form, or subjects have not explicitly asked to withdraw from the study, but no longer undergo test and lost to follow-up, also belonging to " withdraw " (or "drop out"). The reasons for their withdrawal should be understood as much as possible and recorded. Such as consciously feel intolerable to some adverse reactions; unable to continue to receive clinical study due to other reasons; or lost to follow-up without explaining the reason, etc.

3）Handling of withdrawal cases

Subjects, unwilling to continue to participate in clinical research, have the right to withdraw from the study at any time of the study according to the provisions of the informed consent form, or subjects have not explicitly asked to withdraw from the study, but no longer undergo test and lost to follow-up, also belonging to " withdraw " (or "drop out"). The reasons for their withdrawal should be understood as much as possible and recorded. Such as consciously feel intolerable to some adverse reactions; unable to continue to receive clinical study due to other reasons; or lost to follow-up without explaining the reason, etc. Regardless of the reason, for withdrawal cases, the case report form should be retained, and the last examination result transferred as the final result, and full data analysis of the efficacy and

adverse reactions should be conducted.

All study-related toxicity and serious adverse events (SAE) that existed at the time the study was discontinued must be followed up to their resolved, unless, according to the investigator's opinion, the condition cannot be remitted because of the subject's disease itself.

After the subject terminates the study treatment, the investigator must follow up all existing or new AEs during the study period. And report all new AEs and SAEs that occurred within this period of time (if an SAE, it must be reported to the sponsor in time, and tracked until the above-mentioned adverse events are resolved.) After subject terminates the study, the investigator must immediately notify the sponsor. Any SAE needs to contact the sponsor in time with the corresponding SAE reporting process.

There will be no replacement of withdrawn patients.

3.5 Early Termination of Study/ Closure of Study Center

The sponsor has the right to terminate this study at any time, and the sponsor and the investigator have the right to close the study center at any time. Of course, this situation can only be implemented after mutual negotiation. When terminating the study, the independent ethics committee (IEC) and the institutional review board (IRB) must be reported. The ethics committee has the right to suspend or terminate clinical trials that are not implemented in accordance with relevant requirements or that the subjects have suffered unexpectedly severe damage. When the study is terminated early or the study center is closed early, all study materials (except for the documents that must be kept in the center) must be returned to the sponsor. The investigator must keep other documents until notified by the sponsor to destroy it. The reasons leading to the early termination of the trial or the closure of the study center can be, but not limited to, the following reasons:

- New information leads to unfavorable risk-benefit assessments of the investigational drug, for example, due to:
  - The investigational drug lacks efficacy, whether in this study or other studies;
  - The occurrence of significant previously unknown adverse reactions or unexpectedly higher severity/incidence of known adverse reactions; or
  - Other adverse safety findings, including clinical examination and non-clinical manifestations;
- The sponsor believes that it is unreasonable to continue the above study due to Health care, ethical, or commercial reasons;
- It is unlikely that the study will be completed within an acceptable time frame due to the difficulties in enrolling subjects;
- Suspended or terminated at the request of the health authority.

3.6 Definition of The End of the Study

The end of the study is defined as the last subject who completes his/her last visit, unless the end of the study is for a reason in Section 3.5.

4. Study Design

4.1 Study Type and Design Principle

A Prospective, within patient controlled multicenter study.

This study includes 3 regular visits: screening visit(-2w), cystoscopic examination (day 0), safety follow-up(1w). Study design as below:

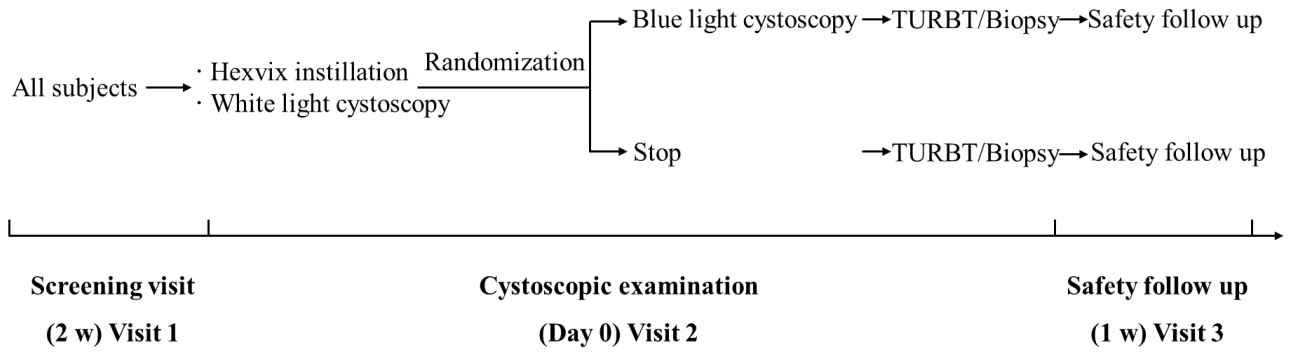


Fig2. Study design

At the start of the study, a minimum of four subjects included at each center will be training subjects. These subjects will receive the Hexvix administration and undergo white and blue light cystoscopy with tumor resection as below. They will receive the same safety follow up as all the other included patients, after completing the safety follow-up for 1 week, the patients will be treated according to hospital's clinical routine by the Investigator. These patients are not part of the efficacy analyses.

To reduce possible bias in assessment of the objectives, a small number of subjects will be randomized to not continue with Hexvix blue light cystoscopy following white light cystoscopy.

Consented, eligible subjects (Visit 1) will be instilled with 50 mL Hexvix 8 mM solution for one hour. After bladder evacuation, the following procedure will be utilized to accomplish the cystoscopic examination of each subject：

1. Turn on the white light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under white light, record lesion number, size and location.
2. Randomization:
   a) If the patient is not randomized to undergo blue light mapping, proceed to step 3.
   b) If the patient is randomized to continue with blue light mapping, or subjects for investigator training procedure, then they will undergo blue light cystoscopy. Turn to the blue light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under blue light, record lesion number, size and location.
3. All papillary lesions detected will be resected using TURBT and all flat and suspicious lesions detected will be biopsied. The lesions resected and biopsied should be marked and pathologically examined separately. For patients randomized to undergo blue light cystoscopy and for training patients, the completeness of the resection should always be checked under blue light before finalizing the TURBT procedure until it is ensured that all lesions and

suspicious areas are completely resected. Both biopsied and resected tissue will be examined by the local pathologist, then evaluated by independent and blinded central pathologists. Central pathology results will be used as reference standard in the study efficacy endpoints.

All subjects (including the training patients) will receive a safety follow-up at day 7 (visit 3) after day 0 cystoscopy (visit 2), after completing the safety follow-up for 1 week, the patients will be treated according to hospital routines by investigator.

Training subjects are not included in the randomization procedure and efficacy analysis, but included in the safety analysis.

4.2 Randomization and Blinding

In this trial, a central random system is used for randomization, subjects will be randomized by an interactive web response system (IWRS) automatically according to grouping sequences to reduce study bias caused by sampling error. The random table is generated by an independent statistician or designated personnel, which is generated by the SAS software based on the number of seeds and blocks pre-set. A block randomization design stratified by sites is adopted. Subject information will be entered by the investigators into the IWRS after verification of inclusion/exclusion criteria. After all subjects undergo Hexvix administration for one hour and then undergo a white light cystoscopy inspection including mapping of the bladder (record lesion number, size and location), subjects will be automatically randomized by the system and grouping information will be feedback to the investigators whether the investigator should continue with a blue light inspection, mapping (record the lesion number, size and location) and biopsy/TURBT (in the same procedure) or to stop the procedure and receive standard treatment by clicking the “Randomization” button in the IWRS. Throughout the trial, the investigators will not be able to modify the group information of subjects.

At each center the Investigator will be blinded to the number of subjects not continuing with Hexvix cystoscopy. A number of subjects (how many should not be known by the investigators) will not continue with Hexvix cystoscopy and these subjects will be distributed randomly among all the centers.

For any subject who has completed the randomization but has dropped out of the trial prior to the initiation of treatment will retain their randomization number (the randomization number assigned to the subject will not be reused). In addition, there will be no replacement for subjects who withdraw early from this clinical trial.

At the start of the study, a minimum of four subjects included at each center will be training subjects. These subjects will undergo Hexvix administration and white and blue light cystoscopy and will have the same safety follow up as all the other included, and treated according to hospital routine practice by the investigator. These subjects should not be included in the randomization procedure, and the subjects will receive subject numbers from a separate series of numbers.

4.3 Study Procedure and Stage

Study will be conducted as study procedures and flow chart in this chapter.

4.3.1 Diagnosis and Pre-treatment Evaluation (visit1)

Pre-treatment evaluation at Visit 1 will only be performed after the patient has agreed to participate,

has signed and dated the informed consent form. No treatment will be initiated before the informed consent has been given.

Pre-treatment evaluation will be performed according to the inclusion and exclusion criteria, including：

1. Patient informed consent.

2. Record demography information (gender, age, ethnicity, height, weight, body mass index, and history of allergies, drug abuse, smoking, alcohol abuse, and blood donation), medical history, and surgery history.

3. Record medication history.

4. Vital signs include: body temperature, sitting blood pressure, heart rate, and breathing rate. Vital signs should be measured when the investigator judges that the subject's condition is stable.

5. Physical examination: general conditions, head and neck, lymph nodes, skin, chest, abdomen, musculoskeletal system (including limbs and spine) and nervous system.

6. Pregnancy test (only for women of childbearing age): The pregnancy test for women of childbearing age during the screening period must be negative. If the subject has undergone a pregnancy test within 7 days before the administration, visit 2 can no longer perform the test. During the study period, urine pregnancy test can be performed as needed. If the urine pregnancy result is positive, a serum pregnancy test is required to confirm. If it is confirmed positive, the subject needs to withdraw from the test, and the investigator will continue to follow up the subject until the end of the pregnancy.

Note: Women of childbearing age must take effective contraceptive measures during the study period.

7. Review the inclusion and exclusion criteria.

8. Record complications, adverse events and concomitant medications/procedures.

4.3.2 Treatment (visit2)

Following successful completion of the pre-treatment evaluations, subjects will continue intoVisit 2. Visit 2 should take place within 14 days of Visit 1 and can be combined with Visit 1.

The following examinations will be performed at Visit 2：

1. Vital signs include: body temperature, sitting blood pressure, heart rate, and breathing rate. Vital signs should be measured when the investigator judges that the subject's condition is stable. Note: Vital signs should be examined before and after surgery.

2. Physical examination: general conditions, head and neck, lymph nodes, skin, chest, abdomen, musculoskeletal system (including limbs and spine) and nervous system.

3. Pregnancy test (only for women of childbearing age): If the subject has undergone a pregnancy test within 7 days before the administration, visit 2 can no longer perform the test. During the study period, urine pregnancy test can be performed as needed. If the urine pregnancy result is positive, a serum pregnancy test is required to confirm. If it is confirmed positive, the subject needs to withdraw from the test, and the investigator will continue to follow up the subject until

the end of the pregnancy.

Note: Women of childbearing age must take effective contraceptive measures during the study period.

4. Assessment of bladder sympotoms before Hexvix instillation.

5. Urine cytology before Hexvix instillation.

6. Hexvix instillation.

7. White light cystoscopy and lesion evaluation/mapping.

8. Randomization.

9. Randomization out or blue light cystoscopy with lesion evaluation/mapping.

10. Biopsy/TURBT/histology.

11. Record complication, adverse events and concomitant medications/procedures.

4.3.2.1 Hexvix instillation Cystoscopy Procedure

1）Instillation

All subjects will have a catheter inserted into their bladder to administer Hexvix solution. The bladder should be evacuated before administering the Hexvix solution. A 50 mL volume of Hexvix 8 mM will then be administered through the catheter. The catheter will be removed, and the subject asked to retain the fluid for 1 hour.

At the end of the instillation period, the subject will be given either local or general anesthesia at the discretion of the Investigator, and the bladder will be evacuated after retaining the Hexvix fluid for 1 hour.

Cystoscopy should not be earlier than 60 minutes after Hexvix instillation to allow tumor cells to synthesize sufficient amount of photoactive porphyrin. The cystoscopic examination should start no more than 3 hours after the start of bladder instillation.

Subjects who fail to retain the Hexvix solution for 60 minutes will complete the procedure, however, cystoscopic examination should not be performed before 60 minutes after instillation.

Cytology will be obtained before Hexvix instillation for all patients.

2）Cystoscopy

All subjects will receive bladder instillation with 50 mL Hexvix 8 mM solution for one hour. After bladder evacuation, cystoscopic examination performed on each subject using following procedures:

1. Turn on the white light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under white light, record lesion number, size and location.

2. Randomization:

a) If the patient is not randomized to undergo blue light mapping, proceed to step 3.

b) If the patient is randomized to continue with blue light mapping, or subjects for

investigator training procedure, then they will undergo blue light cystoscopy. Turn to the blue light. Inspection of the bladder and mapping of all papillary lesions and flat and suspicious lesions seen under blue light, record lesion number, size and location.

3. All papillary lesions detected will be resected using TURBT and all flat and suspicious lesions detected will be biopsied. The lesions resected and biopsied should be marked and pathologically examined separately. For patients randomized to undergo blue light cystoscopy and for training patients, the completeness of the resection should always be checked under blue light before finalizing the TURBT procedure until it is ensured that all lesions and suspicious areas are completely resected. Both biopsied and resected tissue will be examined by the local pathologist, then evaluated by independent and blinded central pathologists. Central pathology results will be used as reference standard in the study efficacy endpoints.

Registration of lesions on the bladder chart will include presence of lesion, type (papillary, or flat), number of lesions and location (bladder neck anterior, trigone, around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall and bladder neck posterior).

The cystoscopy will be videotaped, and the video will be used as the source data for the cystoscopy procedure. The cystoscopy video recording of all training subjects (at least 4 subjects) per study site will be reviewed by sponsor for site qualification. After sponsor’s written approval, the site can start with cystoscopic examination for randomized subjects.

If assigned investigator and / or sub-investigator failed to fulfil the requirements continuously, more training subjects can be requested and reviewed by the sponsor. It needs to be discussed to see if more trainings can be delivered, or tentatively to evaluate if change of investigator is possible

3）Handling and Interpretation of blue light cystoscopy

When using the blue light cystoscopy, there are several points to consider obtaining the best results. Correct handling of the endoscope is important to optimize the results. False fluorescence may appear and correct interpretation of the fluorescing areas is important.

In general, false fluorescence from normal tissue will be weak and diffuse. The endothelium of blood vessels and inflamed areas may show false fluorescence, but fluorescence from neoplastic lesions will be more intense and usually well demarcated. To avoid false fluorescence and get a brighter picture, the endoscope should be held perpendicular and close to the bladder wall. Tangential light will give false fluorescence. Changing of fluorescence intensity when varying the observation angle indicates false fluorescence, as true fluorescence is persistent. A brighter picture will be achieved using a low magnification if a zoom lens is used. Bleeding will reduce the image brightness and good irrigation should be used. Photo bleaching, which is caused by destruction of the photosensitizer and leads to reduced fluorescence intensity, should be kept at a minimum by avoiding unnecessary delay during inspection and mapping of the bladder. Photo bleaching is normally not a problem during inspection and mapping of the bladder, but may be noticed during extensive use of fluorescence-guided resection. However, regeneration of fluorescence may be seen in areas kept 'in the dark' for a few minutes. To minimize photobleaching, the use of white light should be performed under the lowest possible light intensity. Viewing conditions may be altered by the presence of urine, and the bladder should therefore

be adequately evacuated before starting the procedure together with proper irrigation during the examination. Please ensure that the bladder is sufficiently distended as a folded bladder wall may result in increased fluorescence

4）Biopsy/TURBT/Histology

Biopsies/TURBT will be obtained as part of the cystoscopic procedures. Perform biopsy and resection of all lesions and suspicious areas seen in blue light and white light. Both biopsied and resected tissue will be examined by the local pathologist, then evaluated by independent and blinded central pathologists. Central pathology results will be used as reference standard in the study efficacy endpoints.

4.3.3 Seven Day Safety Follow up (visit 3)

The Investigator will contact the patient seven days after the initial cystoscopy/TURBT to record complications, adverse events and concomitant medication or procedures. This contact may be by telephone.

4.3.4 Unplanned Visits

Temporary visits should be made based on clinical needs. Corresponding laboratory abnormalities and adverse events with significant clinical use should be recorded in the CRF and original data.

5. Investigational Medicinal Product and Device

5.1 Investigational Drug

5.1.1 Drug name, Dosage Form and Specification

Name：	Hexvix (hexaminolevulinate hydrochloride for intravesical solution)
Dosage Form：	Powder
Specification：	Hexvix is supplied as a kit containing a 10 mL glass vial containing 85 mg powder of Hexvix (hexaminolevulinate hydrochloride, HAL HCl) for Intravesical Solution, and a prefilled syringe containing 50 mL solvent for Hexvix.
Administration：	The HAL solution is prepared by reconstituting 85 mg HAL HCL with 50 mL solvent. Instillation of the Hexvix solution into the bladder through a catheter, retaining in bladder for 1 to 3 hours before the cystoscopy. Detailed administration sees drug instructions.
Storage：	Hexvix Kit for Intravesical Solution should be stored at 10-30℃. Detailed storage see the drug instructions.

5.1.2 Administration

Investigational drug: Hexvix (hexaminolevulinate hydrochloride for intravesical solution), bladder instillation, single administration. The HAL solution is prepared by reconstituting 85 mg HAL HCL with 50 mL solvent. Instillation of the HAL solution into the bladder through a catheter, retaining in bladder for 1 hours before the cystoscopy. Detailed administration sees drug instructions.

5.1.3 Packaging

The sponsor or delegate CRO will design the label for investigational drug and perform packaging and labeling according to Good clinical practice (GCP) and applicable regulations.

5.1.4 Labelling

The content of the drug label at least includes the followings:

- Clinical trial drug name, strength and dosage form (For clinical trial use only)
- Sponsor
- Protocol number
- Storage conditions
- Expiry date
- Administration method
- Batch number

5.1.5 Drug Distribution, Recording and Recover

Drugs used in this trial are provided and processed according to with GCP regulations. Special personnel from study site are responsible for receipt, inventory management, medication for each subject, drug recover and maintenance of related records. Study drugs must be distributed in

accordance with the requirements of the protocol. Study drugs are provided by the sponsor in free of charge and distributed to each study site, kept and distributed by special personnel from study site. The "Investigational Drug Registration Form" should be filled in and confirmed by the drug administrator and investigator each time the drug is distributed and recovered.

All investigational drugs provided by the sponsor can only be used in this clinical study, and not for purposes out of this protocol. The investigator must promise not to provide the investigational drug to anyone unrelated to this trial. The investigator is required to keep proper records of all investigational drugs distributed, including the date, quantity, and which subjects used.

Un-used study drugs must be returned to the sponsor or destroyed in accordance with the procedures of the relevant regulatory in effect.

5.2 Photodynamic Diagnostic Equipment (PDD) System

The PDD system used in clinical research, namely Richard Wolf PDD system (System blue), is a complete cystoscopy equipment developed for white light and blue light cystoscopy. The system includes any of the following:

- Camera controller, Camera head, Light source, Light cable
- PANOVIEW blue telescopes

ENDOLIGHT LED blue light source and system blue:

The ENDOLIGHT LED blue light source is intended to be used for PDD. The system enables to use of a white light mode, and a blue light mode enabling fluorescence excitation for PDD.

For the application for PDD, the ENDOLIGHT LED blue light source is equipped with two separate LEDs, one for the “white light mode” with an emission spectrum covering almost the entire visible light range and one for the “blue light mode” with peak emission at about 410 nm. This is used to induce and observe tissue fluorescence after hexvix administration. The different LEDs are activated independently from each other, depending on the desired mode of operation, with only one of the LEDs can be operated at once.

The diagnostic approach is selected and configured using the camera controller in the camera menu, a process that normally takes place once at the start of the application. The user can switch between white light and blue light mode using a mode selection button on the light source, or a button on the camera head. Normally, a user switches between white light and blue light several times during an application.

The Richard Wolf PDD system (System blue) for optical diagnosis has been approved for marketing in the European Union and Japan. PDD system (System blue) has not yet been approved for marketing in China. In conjunction with the photosensitizer used and in blue light mode, the PDD system (System blue) respectively the blue light mode is used as an extension of the white light mode for improved detection of superficial bladder tumors. PDD system (System blue) is prohibited for:

1. The PDD system (System blue) must not be used in patients who are not suitable for white light endoscopy.

2. The following patient groups are not suitable for blue light mode:

- Patients who were treated with chemotherapy or immune therapy within the previous six weeks;
- Patient with a florid infection of the urinary tract;
- Patients who already showed an immunological reaction to one of the photosensitizers used in photodynamic diagnostics.

Type no	Product description	Country	Certificate	Valid since
5525833	LOGIC HD PENDUAL CAMERA HEAD BLUE	EU	501,125	19.08.2016
		Japan	13B1X10183P00046	16.01.2019
5165001	LIGHT SOURCE LED BLUE	EU	900,056a	19.08.2016
		Japan	13B1X10183P00047	08.01.2019
8650514	TELESCOPE BLUE 0°Ø 4MM WL 298MM	EU	441,063e	20.01.2006
		Japan	303AIBZI00003000	16.03.2021
8654531	TELESCOPE BLUE 12°Ø 4MM WL 298MM	EU	441,063e	20.01.2006
		Japan	303AIBZI00003000	16.03.2021
8654522	TELESCOPE BLUE 30°Ø 4MM WL 299MM	EU	441,063e	20.01.2006
		Japan	303AIBZI00003000	16.03.2021
8650515	TELESCOPE BLUE 70°Ø 4MM WL 303MM	EU	441,063e	20.01.2006
		Japan	303AIBZI00003000	16.03.2021

The light detection procedure involves irradiating the bladder wall with blue light. Due to the limited penetration of blue light in the tissue, the photoactivation of PAP only occurs on the surface of bladder wall. The light dose given by PDD system is small, and no complications are expected in rgards to light application in patients who undergo blue fluorescence cystoscopy [22].

The irradiance at the distal end of cystoscope is about 200 mW. Assuming that the typical light diagnostic procedure in the patient lasts about 30 minutes, a total light dose of 360 J is applied to the bladder wall. When uniformly distributed on the bladder wall (about 300 cm^2), a total light dose of about 1.2 J / cm^2 is applied. In a rat study [22], no or slight loss of healthy urothelium and no necrosis of urothelium and lamina propria were observed after perfusion of ALA (1%) and application of 50 J light dose (about 25 J / cm^2). Therefore, the light dose (1.2 J / cm^2) for human diagnostic purposes is not enough to cause any damage to urothelial cells in vivo.

System blue and its components (for PDD blue light cystoscopy) have been proved to have good clinical efficacy and safety in several studies [23-28]. The main risk associated with the application of System blue is the potential failure of cystoscopy examination due to device deficiencies. Due to the strict adherence to all standard design and production safety protocols, the possibility of a technical failure during cystoscopy with the System blue is extremely low. In addition, appropriate measures have been taken to minimize the risk to the study subjects, and if unrecoverable device deficiencies

occurred in some or all components of the System blue during the trial, e.g ①In the case of blue light mode failure, subjects could still be examined by the investigator using the white light mode and resection can be performed in the white light mode; ②In the event of a malfunction of the System blue, the investigator can immediately withdraw the investigational device and do the examination and surgery with their standard equipment they use for all their patients diagnosed with bladder cancer.

6. Treatment of Subjects

6.1 IMP

All eligible subjects well receive instillation of 50 mL Hexvix solution for 1hour

All eligible subjects well receive single administration (visit 2).

6.2 Concomitant Medication

Concomitant medications include any drugs (including prescription drugs, over-the-counter drugs, natural extracts, nutritional supplements, traditional Chinese medicines, etc.) used by the subject from signing the informed consent form (ICF) to the completion of the last visit specified in the flowchart. Note: There is no need to record normal saline. The medications used by subjects during the screening period are recorded as medication history. Any prescription drugs and over-the-counter drugs, herbal medicines, vitamins and nutritional supplements used by the subjects must be reviewed and approved by the investigators. Information on concomitant medications should be recorded in detail.

During the study period, symptomatic treatment drugs that will not affect the efficacy and safety of the study drug can be used in combination, and the medication should be specified in detail.

6.3 Compliance

The investigator must emphasize compliance to the subjects when they agree to the interview.

During the trial, if the subject's compliance is poor, the investigator should find out the reason, actively take corresponding measures (such as emphasizing the importance of protocol compliance to the subject), and fully record the non-compliance, the reason, and the corresponding measures taken.

7. Assessment of Efficacy

All efficacy endpoints assessments will be based on central pathology results, which will be used for statistical comparisons.

7.1 Primary Efficacy Endpoint

The primary efficacy endpoint of this study as below:

- The proportion of patients with histology-confirmed tumors (Ta, T1, or CIS) who have at least one such tumor found by Hexvix but not by white light cystoscopy.

7.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint of this study as below:

- The proportion of patients with one or more CIS lesions detected with Hexvix blue light cystoscopy not by white light cystoscopy.
- The lesion detection rate of Hexvix blue light cystoscopy, compared to white light cystoscopy per lesion type (PUNLMP, CIS, Ta, T1, T2-T4).
- The proportion of false positive lesions detected with Hexvix blue light cystoscopy and white light cystoscopy.

7.3 Central Pathology Evaluation

All efficacy endpoints assessment will be based on central pathology consensus panel results to reduce the difference between the pathological evaluations used in the efficacy analysis.

The WHO 2016 World Health Organization/International Society of Urologic Pathology consensus classification and the Union for International Cancer Prevention (UICC) 2017 8th edition of TNM classification for staging of bladder cancer will be used to grade and stage tumors. Two independent pathologists unaware of the diagnosis of the local pathologist and whether the biopsy came from a lesion seen in white light or blue light or both, provide a pathology diagnosis independently. If the two pathologists agree on the diagnosis, this is the final diagnosis. If they disagree, a third independent pathologist will make a diagnosis without knowing the diagnosis of the two first pathologists. If this diagnosis is in agreement with the diagnosis made by the one of the first pathologists, this result will be the final diagnosis. If the three pathologists disagree on the diagnosis, they will discuss together. If they agree on a diagnosis, this will be the final consensus diagnosis. If they fail to reach agreement, this lesion will be excluded from the statistical analysis.

A histologically confirmed malignancy is a tumor staged/graded as CIS, Ta, T1 orT2-T 4 by the consensus panel. Lesions can be classified to PUNLMP, low grade and high grade.

7.4 Efficacy Parameters

Efficacy parameters recorded in eCRF will be used in both analyses of the primary and secondary endpoints.

7.4.1 Detection of Lesions by White Light Cystoscopy

- Number of lesions and suspicious areas seen.

- Type of lesion and suspicious area seen (flat or papillary).
- Location of lesions and suspicious areas (Bladder neck anterior, trigone, around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall, bladder neck posterior).

7.4.2 Detection of Lesions by Blue Light Cystoscopy

- Number of fluorescent lesions and suspicious areas seen.
- Type of fluorescence lesions and suspicious areas seen (flat or papillary).
- Location of fluorescent lesions and suspicious areas (Bladder neck anterior, trigone,around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral wall, cranial wall, left lateral wall, dome, anterior bladder wall, bladder neck posterior)

7.4.3 Subject Diagnosis

Subject diagnosis will be recorded including the assessments performed. This will include the staging and grading based on the use of cystoscopy, biopsies/histology, cytology, markers and/or other test(s).

8. Assessment of Safety

8.1 Adverse Events

8.1.1 Definition Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient from signing the ICF to the completion of the last visit specified in the flowchart (visit 3) and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Symptoms/signs that begin or worsen in severity and/or frequency after Hexvix instillation will be recorded as AEs in the eCRF.

Examples of adverse events may include the following factors:

- A new sign, symptom, illness, or syndrome
- Worsening of a concomitant disease, sign or symptom at baseline
- An effect of investigational product, including comparator or concomitant medication
- An effect of an invasive procedure required by the protocol
- An accident or injury

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected after the administration of Hexvix. Planned surgical measures permitted by the clinical study protocol, i.e., surgical treatment for bladder cancer, are not adverse events.

8.1.2 Period of Observation

The period of observation is defined as the period from instillation of Hexvix until the end of the study.

8.1.3 Reporting of Adverse Events

All adverse events occurring during the period of screen and observation must be documented on the adverse event form in the eCRF.

A baseline recording of clinical bladder cancer symptoms will be performed before administration of Hexvix. Only symptoms that increase in severity or new symptoms of any illness will be recorded as adverse events in the eCRF.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis. For example, if myocardial infarction is reported as an AE, there is no need to report elevated creatine phosphokinase and abnormal ECG, or other related signs, symptoms, or laboratory values as separate AEs. However, if both occurred in isolation and myocardial

infarction was not diagnosed, then each event would be reported as an AE. In this case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

AEs will be recorded as follows:

- All AEs occurring in the period of observation, whether or not considered related to Hexvix and/or blue light, will be recorded
- All SAEs that are considered related to Hexvix and/or blue light occurring after the period of observation, but before database lock, will be recorded in the eCRF and included in the clinical database

All SAEs that are considered related to Hexvix and/or blue light occurring after database lock will be reported to the sponsor and included in the safety database only. The sponsor will code all adverse events according to current standard dictionary (MedDRA).

8.1.4 Severity of Adverse Events

The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:

Mild	the adverse event is transient and easily tolerated
Moderate	the adverse event causes the patient discomfort and interrupts the patient's usual activities
Severe	the adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening

8.1.5 Relationship of Adverse Event to the Drug

The causality assessment of adverse events will be done by the performing clinical investigator urologist. Relationship to Hexvix and/or blue light will be categorized as "yes" or "no" or "uncertain", of which the "yes" and "uncertain" are considered as Adverse Drug Reaction (ADR):

Yes	an adverse event which after careful examination at the time of evaluation, appears to be related to Hexvix and/or blue light
No	an adverse event which after careful examination at the time of evaluation, is judged to be clearly and incontrovertibly due to extraneous causes (disease, environment, etc) and do not meet the criteria described under "yes"
Uncertain	there is no clear relevance between the event and the time of administration, the event is similar to the known reaction type of the investigational drug, while the same reaction may be caused due to the use of other drugs. Therefore, there is no sufficient basis for the determination.

8.1.6 Outcome of Adverse Events

All adverse events must be followed for a final outcome until the end of the period of observation. Related and/or serious adverse events must be followed until resolved, or at the latest until the database is locked. In case of permanent impairment, the event must be followed until the condition stabilizes and the investigator considers is medically justifiable to terminate follow-up, or until database lock.

For adverse events resulting in death, a full pathologist report should be supplied if possible.

Outcome will be recorded in the eCRF as one of the following:

- Resolved
- Resolving
- Not resolved
- Resolved with sequelae
- Unknown
- Death

8.2 Serious Adverse Events

8.2.1 Definition of Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

1) Results in death

2) Is life threatening, the term “life threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3) Requires inpatient hospitalization or prolongation of existing hospitalization[iii]

4) Results in persistent or significant disability/incapacity[iv]

5) Is a congenital anomaly/birth defect

6) Other medically important condition

In addition, medical and scientific judgment is required to decide if prompt notification is required in other situations, i.e., any event which the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the patient or required intervention to prevent one of the outcomes listed above, or which would suggest any significant hazard, contraindication, side effect or precaution that may be associated with the use of the drug.

8.2.2 Reporting of Serious Adverse Events

All SAEs occurring in the period of observation, whether or not related to the study intervention, must be collected and reported to the sponsor / CRO safety contacts and regulatory authority.

SAE occurring after the period of observation should be reported by the investigator to the sponsor /CRO if the investigator considers the SAE to be causally related to the study intervention.

An SAE report consists of the following:

- SAE form (available in Investigator Site File and electronically)
- Adverse event form
- Concomitant medication form
- Medical history form
- Bladder cancer medical history

The initial report must be as complete as possible, including all items on the SAE form, otherwise the complete SAE form will need to be sent to the sponsor /CRO Security contacts. The SAE form should preferably be completed electronically. The investigator should report SAE to the sponsor /CRO Security contacts via SAE Manager System (preferred) or email to DS-CT@asieris.cn and PPC.China.PV@ppccro.com (when system error) within 24 hours following knowledge of the event.

The investigator should not await additional information to fully document the event before reporting an SAE, although additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained. The investigator is also required to submit follow-up reports until the SAE resolves, or in the case of permanent impairment, until the SAE stabilises.

Information not available at the time of the initial report (e.g., end date for the adverse event or laboratory values received after the report) must be documented as a follow-up report. A new SAE form must be completed, and marked as “Follow-up”.

Details of all SAEs must also be reported on the adverse event form in the eCRF.

If an adverse event initially recorded as non-serious event, becomes serious, this must also be reported within 24 hours following knowledge.

The sponsor will report all SAEs to local health authorities and investigators as required by local regulations and sponsor standard operating procedures (SOPs). The investigator is responsible for reporting SAEs to the Institutional Review Board (IRB) according to local requirements.

8.3 Suspicious and Unexpected Serious Adverse Reactions

8.3.1 Definition of Suspicious and Unexpected Serious Adverse Reactions

Suspicious and unexpected serious adverse reactions (SUSAR) refer to those with the nature and severity of the clinical manifestation beyond the information of the existing materials such as the Investigator's Brochure of the investigational drug.

8.3.2 Reporting of Suspicious and Unexpected Serious Adverse Reactions

There is no time limit for the collection of serious adverse events judged to be related to the investigational drug. This means that serious adverse events related to the investigational drug that even occur after the last visit specified in the protocol should still be reported. The reporting method for SUSAR that occurs after the clinical trial is completed and before the approval conclusion is obtained is consistent with that before the trial is completed.

The sponsor and/or sponsor representative will report SUSARs to health authorities, ethics committees and investigators, etc. as required by local regulations, sponsor standard operating procedures (SOPs) and other internal references (e.g. Safety Management Plan).

8.4 Reporting of Pregnancies

If a patient or patient partner becomes pregnant during study participation, the investigator must report the pregnancy to the sponsor / CRO safety contacts within 24 hours following knowledge of the pregnancy, reporting method is the same as the SAEs above. The pregnancy should also be recorded in the eCRF.

Patients who become pregnant during study participation will be followed until completion of pregnancy. The pregnancy outcome information must be submitted to the sponsor as soon as it becomes available by completing the pregnancy surveillance form part II. The investigator is responsible for reporting any pregnancies to the IRB.

8.5 Sensitization Risks and Management Measures

Hexvix® has the potential to cause rapid-onset severe allergic reactions / hypersensitivity reactions, for which the Sponsor has developed a risk management plan and is managing this as a "significant identified risk".

The routine risk preventive measures that the Sponsor takes concerning this risk are as follows:

1. In this clinical trial, subjects with allergy to hexaminolevulinate hydrochloride or a similar compound will be excluded;

2. The information on the safety profile of Hexvix concerning allergy occurring in preclinical studies, clinical studies and postmarketing exposure is fully described and prompted in the investigator brochure.

3. Information on risks is provided in the clinical use instructions:【Contraindications】Hypersensitivity to the active substance or to any of the excipients. Porphyria. 【Special warnings and precautions for use】The possibility of hypersensitivity including serious anaphylactic/anaphylactoid reactions should always be considered. Advanced life support facilities should be readily available. 【Undesirable effects】Adverse reactions from clinical trials and spontaneous reporting: immune system disorders - anaphylactoid shock.

9. Data Management

9.1 Data Management Process

Sponsor or delegate CRO is responsible for the study data management to ensure the authenticity, integrity, privacy and traceability of clinical trial data.

9.2 Database Design and Establishment

The eCRF database is constructed by Sponsor or delegate CRO. The database should manage data traces such as system login, data entry, modification, or deletion, and the establishment of the database shall adopt the CDISC standard.

9.3 Data Entry

Information will be entered into the Electronic Data Capture (EDC) database by the investigator or a person authorized by the investigator within 3-5 working days after completion of the visit. And strictly follow the "what you see is what you record" principle of data entry. After the original data is entered, any changes made to the eCRF are automatically recorded in the system.

9.4 DataVerification

According to the finalized Data Verification Plan (DVP), Data Manager (DM) will set up Data logic verification procedures in the EDC system.

After data entry into the EDC system, if there is any illogical data, the system check will start operation and trigger the challenge. These queries need to be reviewed and answered by the investigator or a person authorized by the investigator. When the updated data makes the logical check no longer valid, the data challenge is closed immediately; If the site confirms the data and provides a response, the DM will review the response information. When the reason is reasonable, turn off the data query; When the data problem is not solved, DM can continue to communicate with the site by adding data query until the final solution.

Generate subject data lists/reports programmatically to support manual data verification throughout the study. When there is data that needs to be clarified/verified/confirmed by the researcher, human questioning can be added to the EDC system. The data manager should confirm that all queries have been resolved and the investigator should complete the electronic signature in the EDC system to ensure the integrity and accuracy of the subject data in the EDC system.

9.5 Medical Coding

The data manager (DM) is responsible for the medical coding of this study. The code includes medical history, concomitant medications, and adverse events.

Previous medical history and adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The concomitant drug use was coded by the World Health Organization Drug Dictionary (WHO DD), which adopted the version confirmed by the sponsor.

In the process of coding, DM will ask investigators to verify and confirm any data problems that cannot be encoded due to improper, inaccurate or vague medical terms.

Before the database is locked, DM will send a medical coding report to the sponsor and it will be reviewed by the sponsor.

10. Statistical Considerations

10.1 General Principle

The Statistical Analysis Plan is prepared by the Biostatistician and the Principal Investigator according to the study protocol and will be finalized and documented prior to the first database lock. Detailed statistical analysis methods will also be specified in the statistical analysis plan.

All statistical analyses will be completed using SAS version 9.4 or higher. See statistical analysis plan for specific statistical methods.

Continuous variables will be described by mean, standard deviation, median, first quartile, third quartile, maximum and minimum.

Categorical variables will be described by frequency and percentage. If necessary, 95% confidence interval (95% CI) of the percentage will be calculated.

10.2 Determination of Sample Size

Approximately 380 subjects will participate in the study and will continue until 94 subjects with pathologically confirmed of bladder cancer at Ta, T1, and CIS stages.

The sample size calculation for this study is as follows:

The primary efficacy endpoint of this study is "The proportion of patients with histology-confirmed tumors (Ta, T1, or CIS) who have at least one such tumor found by Hexvix but not by white light cystoscopy. A proportion of 10% is considered clinically significant, and if the actual proportion is 20%, that is, the null hypothesis is P null hypothesis = 10% and the alternative hypothesis is P alternative hypothesis = 20%, a total of 94 subjects with pathologically confirmed Ta, T1, and CIS stage bladder cancer are required at a one-sided significance level of 0.025 with 80% power based on an exact test for one proportion.

Assuming that 35% of subjects will have bladder cancer after Hexvix-assisted blue light cystoscopy and/or white light cystoscopy, bladder cancer with Ta, T1 and CIS stage accounting for 75%, 359 subjects are expected to be enrolled in this trial. Considering the 5% drop-out rate, a total of about 380 subjects are required. The study will continue until 94 subjects have bladder cancer after Hexvix-assisted blue light cystoscopy and/or white light cystoscopy and are pathologically confirmed as Ta, T1, and CIS stage bladder cancer.

Note: A minimum of 4 subjects included at each center will be training subjects, and those training subjects are in addition to the estimated sample size. Moreover, training subjects are not included in the randomization procedure and efficacy endpoints analysis set, but included in the safety analysis set.

10.3 Statistical Analysis Populations

10.3.1 Safety Set

All subjects who receive Hexvix instillation will be included in the safety population (including training subjects for investigators).

10.3.2 Full Analysis Set

10.3.2.1 Full Analysis Set (FAS)

All secondary efficacy analysis will be based on full analysis set (FAS). Subjects who receive Hexvix instillation and undergo blue light cystoscopy will be included in FAS. Efficacy data of subjects who received Hexvix and white light cystoscopy but did not continue with blue light cystoscopy will be shown in individual table. Training patients who receive Hexvix and white light cystoscopy and blue light cystoscopy and have evaluable data will not be included in FAS.

10.3.2.2 Modified Full Analysis Set (mFAS)

Primary efficay analysis will be based on modified full analysis set (mFAS). Subjects who receive Hexvix instillation and undergo blue light cystoscopy, and are pathologically confirmed as Ta, T1, and CIS stage bladder cancer will be included in mFAS. Efficacy data of subjects who received Hexvix and white light cystoscopy but did not continue with blue light cystoscopy will not be included in mFAS. Training patients who receive Hexvix and white light cystoscopy and blue light cystoscopy and have evaluable data will not be included in mFAS.

10.3.3 Per Protocol Set

10.3.3.1 Per Protocol Set (PPS)

The analysis of secondary efficacy endpoints will be based on the per protocol set (PPS). PPS is a subset of FAS. A subject will be excluded from the PPS for the following reasons:

- Failure to fulfill inclusion criteria / exclusion criteria but still entered into the study.
- Failure to retain the Hexvix solution for at least 30 minutes.

Protocol violations that are thought to affect the result of the cystoscopy or the histologic result may result in subjects being excluded from the PPS (will be documented before data base lock).

10.3.3.2 Modified Per Protocol Set (mPPS)

The analysis of primary efficacy endpoints will be based on the modified per protocol set (mPPS). mPPS is a subset of mFAS. A subject will be excluded from the mPPS for the following reasons:

- Failure to fulfill inclusion criteria / exclusion criteria but still entered into the study.
- Failure to retain the Hexvix solution for at least 30 minutes.
- Subjects who protocol deviations that affected the evaluation of primary endpoint.

Protocol violations that are thought to affect the result of the cystoscopy or the histologic result may result in subjects being excluded from the mPPS (will be documented before data base lock).

The mPPS analysis is done as a supportive analysis of the primary efficacy endpoints, and will show if the exclusion of subjects from the mFAS will affect the overall conclusions of the results.

10.4 Statistical Analysis Method

10.4.1 Subject Disposion and Baseline Characteristic Analysis

All baseline and demographic data analysis will be performed on the basis of FAS and mFAS.

List the information of subjects who failed screening, including screening number and reasons for

screening failure. Subjects who failed screening will be summarized, including number of screen failures, number of screen failures, and percentage of each screen failure reason.

The number of subjects enrolled in the study, the number/percentage of subjects undergoing white and blue light cystoscopy, the number/percentage of subjects included in the efficacy, safety evaluations, the number/percentage of subjects completing each period of the study, and the reasons for withdrawal will be summarized.

Listings of demographic data and baseline characteristics will be provided. Descriptive statistics will be performed for all demographic data and baseline characteristics (e.g., gender, age, ethnicity, height, weight, previous medical history, current medical history, medication history, urine cytology).

Details will be described in the statistical analysis plan.

10.4.2 Efficacy Ananlyses

Efficacy endpoint analysis will be based on FAS/mFAS and PPS/mPPS.

10.4.2.1 Primary Efficacy Endpoint

The analysis on primary efficacy endpoint will be performed on the basis of mFAS and mPPS. Primary efficacy endpoint will be analyzed based on subjects who received Hexvix instillation and continue with blue light cystoscopy, and are pathologically confirmed as Ta, T1, and CIS stage bladder cancer. Training patients will not be included.

For analysis of the primary efficacy endpoint (The proportion of patients with histology-confirmed tumors (Ta, T1, or CIS) who have at least one such tumor found by Hexvix but not by white light cystoscopy), an exact test for single proportion, using the cumulative binominal distribution, with a significance level of 0.025 (1-sided) will be used, based on the mFAS and mPPS, and the 95% confidence interval for the detection rate will be calculated.

10.4.2.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints analysis will be based on FAS and PPS.

Secondary efficacy endpoints will be analyzed descriptively, including event rate and 95% confidence intervals based on the FAS and PPS. Exact 95% confidence interval will be calculated similarly to that of the primary efficacy endpoint. But no formal statsitical inference will be made to the secondary efficacy endpoints.

If the establishment of confidence intervals is based on biopsy/TURBT data, Bladder biopsy/TURBT data should be assumed to be independent of each other.

Efficacy data will be tabulated in detail.

10.4.3 Safety Analysis

Safety analysis will be based on safety set.

The reported adverse events (including local reactions) will be coded according to MedDRA terminology. The events will be tabulated by System Organ Class and by Preferred term.

Adverse events will also be tabulated versus severity and relation to treatment.

Physical examination and vital signs at each visit will be presented using descriptive statistics.

10.4.3.1 Adverse Event

Adverse event will be coded according to MedDRA terminology, using descriptive statistics and annlysis by System Organ Class and by Preferred term.

The overall incidence of adverse events, adverse reactions, treatment-emergent adverse events, study drug-related adverse events, significant adverse events, serious adverse events, and the incidence by SOC/PT will be calculated. The number and number of patients with treatment-emergent adverse events, adverse events will be summarized by SOC and severity. Adverse events, adverse reactions, treatment-emergent adverse events, adverse events related to the study drug, significant adverse events and serious adverse events should be listed in detail.

10.4.3.2 Pregnancy Test

For pregnancy tests, results were summarized and tabulated in detail using descriptive statistics. See general principles for analytical methods.

10.4.3.3 Other Safety Information（Including Vital Signs and Physical Examination, Device Events）

The results of vital signs and physical examination indicators at each visit will be analyzed and listed in detail. See general principles for analytical methods. Details will be described in the statistical analysis plan.

10.4.4 Interim Analysis

No interim analysis is planned for this study.

11. Management of Clinical Trials

11.1 Statement

The clinical trial will be conducted in accordance with the sponsor's and CRO's standard of practices and sponsor is responsible to ensure CRO’s standard of practices, which are designed to ensure that the trial is conducted in accordance with the requirements of the Declaration of Helsinki, China's GCP and pharmaceutical Clinical Trial regulations.

In signing the protocol, the investigator agrees to follow the instructions and procedures set forth in the Protocol and to adhere to the principle of the ICH GCP for quality management of Pharmaceutical Clinical Trials and all the principles governing local regulations and medical study.

11.2 Ethics

This study is designed and prepared in accordance with the Declaration of Helsinki of the World Medical Association, considering the rights and welfare of subjects in. The principal investigator or investigator of the clinical trial explains to the subjects the purpose of the trial and all the potential possibilities, and the subjects who voluntarily agree to participate in the clinical trial and sign the informed consent form will be the subjects.

Clinical trial investigators and participants should properly analyze and understand the study plan and be able to prepare in advance, such as response to unexpected adverse events, required reporting and adequate training. Clinical investigators conducting clinical trials are required to comply with the regulations for Clinical Trials of Investigational Drugs (SFDA Order No. 5).

The principal investigator and the study participants should comply with the content in the study protocol and scientifically maintain the current recognized technical level to conduct the trial.

In accordance with national policies and regulations, the investigator provides relevant trial documents to the ethics committee.

A copy of the IRB approval, along with a list of review documents, must be submitted to the sponsor before the drug is shipped to the investigator. The Ethics Committee approval document should be accompanied by a list of all committee members participating in the discussion of the approval document and their respective responsibilities.

After the study protocol is approved by the ethics committee, the sponsor will submit the clinical study protocol to the NMPA for filing.

Clinical trials must be approved by the ethics committee and the pharmaceutical administration before they can begin.

Changes to the study protocol should be submitted to the ethics committee for approval and informed to health authorities as required locally.

During the period of a clinical study, the investigator must inform the ethics committee of any serious adverse event or unexpected adverse events related to the safety of the clinical study that may affect the safety of patients and the conduct of the study.

11.3 Check the Original Records

All data obtained during clinical studies must be handled appropriately by the investigator to ensure the rights and privacy of patients participating in clinical studies. The investigator must consent to the monitor/auditor/inspector's access and review of the clinical study data as required to verify the accuracy of the original data and to understand the progress of the study. If it is not possible to verify the original records, the investigator should agree to assist the monitor/auditor/inspector in further verifying the quality control of the data.

11.4 Quality Assurance and Audit

All drugs and materials used in clinical study must be quality controlled. The sponsor, the sponsor's authorized personnel or the relevant medical regulatory agency should have the right to audit the clinical study in order to ensure the authenticity of the clinical study data and to comply with the provisions of the clinical study protocol.

The study will be organized, conducted and reported in accordance with the protocol, sponsor and CRO's standard operating procedures. In ICH E6(R2), Quality assurance (QA) is defined as "planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented(recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements". Sponsor QA work will be carried out in accordance with the study audit plan. ICH E6, Section 5.19.3 (b), provides that sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).QA work can be transfered to a CRO or an independent consultancy. Require the investigator to support the audit, attend the audit as required, and allow the investigator direct access to raw data/documentation, including all medical records, study-related documents and correspondence, and informed consent documents for the clinical trial. Clinical study subjects will be informed of the clinical study review process, but subject privacy and data will be strictly protected.

11.5 Informed Consent

It is the investigator's responsibility to explain to each subject the purpose, method, benefits and potential risks of the clinical trial, alternative treatment options, and the subject's rights and obligations in accordance with the Declaration of Helsinki. Subjects should be informed that they have the right to withdraw from the study at any time and that their personal interests will not be harmed. An informed consent form signed by the subject must be obtained prior to any procedure related to the clinical trial.

Written informed consent must be given orally. Informed consent must be dated and signed by each subject or his or her legal guardian or agent. The signed informed consent and information pages will be retained by the subject and another signed informed consent will be retained and retained as a study file by the subject prior to the commencement of any study related procedures.

The consent form must be approved and signed by the subject prior to the commencement of any study related procedures. Prior to obtaining informed consent, the investigator or his designee shall provide the subject with sufficient time and opportunity to ask about the details of the study and to decide whether to participate in the study. The process of informed consent should be recorded in the course record on the day of screening visit.

The investigator is responsible for the informed consent process. If any information regarding the subject's willingness to continue participating in the study is obtained during the study, the written informed consent must be updated and given to the subject to confirm the subject's willingness to continue participating. The revised informed consent is provided to subjects only after ethical approval is obtained.

By signing the informed consent, the subject/patient must also agree to allow the sponsor, fda, auditors, and/or clinical trial monitors authorized by the sponsor to review the obtained raw data related to the clinical study, and the auditor must abide by the confidentiality statement.

11.6 Modification of Clinical Protocols

After the approval of the ethics Committee, if there is any major modification during the implementation of the program, the principal researcher of the responsible unit shall write the "Program Modification Manual" and sign it. At the same time, it can be implemented only after the approval of the ethics committee.

Any non-principled amendment shall be decided by the main researchers, statisticians and sponsoring units of the responsible units through joint discussion, and shall be notified to other participating units. The Investigator shall not perform any protocol departure or change without the sponsor's consent and prior EC review and written approval (ICH E6 4.5.2).

Any changes to the program, whether major or non-major, are required to be made in writing. Any substantive protocol modification that would affect the subject's safety, study scope, or scientific quality of this study would require approval from the EC of all study centers. In order to protect the safety of all subjects in the study, the above requirements shall not prevent the investigator or sponsor from taking any urgent measures. If the investigator considers that an immediate protocol change is necessary for safety reasons, he/she must promptly notify the sponsor's designated institution and the EC in accordance with the policies, local regulations and policies of the EC approving the study. Changes affecting study management only do not require substantive protocol revision or EC approval, but such changes must be notified to the EC. In these cases, the sponsor will send an official letter to the EC detailing these changes.

11.7 Protocol Deviation

The investigator should follow the clinical trial protocol approved by the ethics committee and comply with the GCP regulations to conduct the clinical trial. Protocol was developed to enable the investigator to comply with ICH E6 (R2), Section 4. During the study, the investigator should not deviate from the protocol unless urgent measures are taken to eliminate direct harmness to the subject. The investigator should consult with the monitor (and the IRB or IEC, if necessary) to determine appropriate action in the event of other unexpected circumstances that require departure from protocol procedures.

The site should record all protocol deviations in the subject's original data, including but not limited to the occurrence time of protocol deviations, discovery time, event description and measures taken, etc. In the event of serious protocol deviation, the center should promptly notify the medical monitor, Clinical Research associate (CRA), IRB, or EC.

11.8 Electronic Case Report Form（eCRF）

The CRO database programmer will set up the eCRF and approved by sponsor. Only appropriate identification codes (e.g., study center number and subject number) and initials are used to identify individual subjects on the eCRF. The eCRF is used to record the clinical study data of the subject and is an integral part of the study and related study reports, so the entry must be accurate and complete. The eCRF is entered into the EDC system by the investigator or authorizer (indicated on the study authorization form). All data entry must be ensured to be completed and stored. The investigator must declare that all information in the eCRF is authentic by electronic signature.

In clinical studies, the eCRF is usually completed within 3-5 business days after each visit to record the subject's condition.

Medical records and other records related to the subjects' disease progression during the study will be maintained by the investigator. These records should include original or photocopies of laboratory data and other medical test results, which must be kept at the center along with the subject's medical records.

11.9 Monitoring

The sponsor or delegate CRO responsible monitoring

Prior to selecting a center to participate in the study, a center selection visit will be conducted to confirm that the center, instruments and staff meet protocol requirements and GCP guidelines.

During the study, the monitor conducted regular on-site monitoring of the center, and each monitoring should record the visit date on the central visit record of the center.

The monitor's activities for study monitoring includes:

- Study center initiation visits, collect and distribute necessary pre-study documents; provide guidance to investigators and center staff on protocols, study procedures and expectations; Obtain the investigator's assurance that the study will be conducted in accordance with the study requirements and GCP guidelines, and introduce the study materials to the investigator and corresponding study staff.
- Monitoring visit: As required by the GCP, the monitor participating in the current study were fully aware of confidentiality issues and compared the data in the eCRF with data from hospital or clinical records (raw data). Prior to the start of the study, the monitor should discuss with the investigator the specific items required as source data, determine the nature and location of all source data to ensure that the sponsor or investigator knows the source of the source data used to complete the eCRF table, and the sponsor authorises the monitor's right to check; All observations and findings made during an monitoring must be verifiable. If electronic records are kept at the study site, methods of verification must be discussed with study members.

The source material must be at least verifiable:

- Subject identity, eligibility and participation;
- Appropriate informed consent procedures;
- Visit date;

- Recording of safety and efficacy parameters;
- Adequate reporting and visits of adverse events;
- treatment with concomitant drugs;
- Records of receipt/distribution/return of drugs;
- Research drug administration information;
- Subject's completion of treatment, termination of treatment or withdrawal from the study, and appropriate reasons;
- The data is true, accurate and complete;
- The safety and rights of the subjects are protected;
- The investigator implements compliance with the currently approved protocol, GCP, and all relevant regulatory requirements.

- Objectives to be achieved in the inspection include:
- Review and evaluate study progress
- Review collected study data
- Implement source document verification process

During the study period, the monitor will have direct access to all relevant documents with the consent of the investigator, and the investigator will ensure that himself and the investigator meet regularly with the monitor to discuss findings from the visit and any relevant issues.

11.10 Intellectual Property Rights

All information received from the trial sponsor is the intellectual property of the trial sponsor. Therefore, the clinical trial investigator and all other relevant personnel must keep it strictly confidential and should not disclose it to any third party without the prior consent of the trial sponsor.

11.11 Subject Privacy

Investigators must ensure that the privacy of clinical trial subjects is maintained. In all documents submitted to the sponsor, clinical trial subjects should be identified only by the clinical trial screening/randomization number and initials, and not by name. The investigator must maintain the name and address of the subject and the enrollment form corresponding to the drug number of the clinical study. These entry forms are kept strictly confidential by the investigator and cannot be submitted to the sponsor.

12. Publication

Photocure ASA, as the sponsor, has exclusive rights to this study. The authors and contributions will reflect the collaboration between multiple researchers and the staff of the research base and Photocure ASA. Authors should be determined before writing a manuscript. Because many sites participating in this study, individual publications are not allowed until the final report of the multicenter study is completed, unless the agreement are obtained from Photocure ASA. Photocure ASA has the final say on the manuscript and publication.

13. Data preservation

13.1 Source Data and Source files

In this trial, the source data includes records of clinical findings, observations, and other relevant activities needed for reconstructing and evaluating the clinical trial. Raw data is contained in the source file.

Source documents involved in clinical studies are original records, documents and data (such as hospital records, medical images, laboratory records, memos, subject diaries or evaluation forms, drug delivery records, data automatically recorded by instruments, microfilm, photographic plates, magnetic media, X-rays, subject files, Documents and records relating to clinical trials maintained by pharmacies, laboratories and medical technology departments, including certified copies, etc. The source files must be preserved to support the information provided in the eCRF.

13.2 Data preservation of the sites

13.2.1 Information related to the ethics committee

The data preservation staff of the research unit shall retain the minutes and summaries of the ERC meetings until 5 years after the termination or completion of the study. If the sponsor wishes to stay longer, the two sides will discuss and decide how long and how to stay. In the event of any changes in documentation retention by the test unit, the person or researcher responsible for documentation retention should contact the sponsor.

13.2.2 Material related to trial conduction

The following documents must be retained by the data preservation staff of the sites for minimum 5 years after the approval of the investigational drug for marketing. If the sponsor wishes to stay longer, the two sides will discuss and decide how long and how to stay. In the event of any changes in documen-tation retention by the site, the person or investigator responsible for data retention should contact the sponsor.

- Source material;
- Original or copy of the study contract, informed consent, and other information related to GCP provided by the staff of the site;
- Study protocol, GCP-related data obtained from the ethics committee, or other GCP-related data obtained;
- Records of the administration of the investigational drug and other records related to the conduct of the trial

13.3 Data preservation of the sponsor

The following information (including documents and data) will be retained by the sponsor until 5 years after the trial drug is approved for marketing. A longer shelf life may be required according to relevant regulations. It is the sponsor's responsibility to inform the investigator/site when such data are no longer required to be kept.

- The original or copy of the study protocol, the study contract, the study report, or the

materials related to GCP provided by the sponsor;

- Case report form, GCP related notification, or GCP related data obtained from investigator;
- Monitoring, auditing related records, or other relevant operation records;
- The data obtained in the study
- Relevant records as required by GCP.

14. Reference

【1】 NCCN Guidelines on bladder cancer, version 3, 2020.

【2】 Huang jian et al. Chinese guideline on bladder cancer. 2019.

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