CLINICAL STUDY PROTOCOL

Investigational drug:	**Cysview® for Intravesical Solution**
Investigational device:	**KARL STORZ D-Light C PDD Flexible Videoscope System**
Protocol number:	**PC B308/13** **Blue Light Flexible Cystoscopy with Cysview Study**
Study title:	**A prospective, open, comparative, within patient controlled multicenter phase 3 study of blue light cystoscopy with Cysview and white light cystoscopy using KARL STORZ D-Light C PDD Flexible Videoscope System in detection of bladder cancer in patients with bladder cancer**
Study phase:	**3**
Original protocol:	**29.Apr.2015**
Protocol version:	**Protocol including Amendment 1 FINAL**
Date:	**20.Nov.2015**
Amendment history:	
Amendment #1:	**20.Nov.2015**

Name of sponsor: Photocure ASA
Name of drug and investigational device: Cysview® for Intravesical Solution KARL STORZ D-Light C PDD Flexible Videoscope System
Name of active ingredient: Hexaminolevulinate hydrochloride
Study title: A prospective, open, comparative, within patient controlled multicenter phase 3 study of blue light cystoscopy with Cysview and white light cystoscopy using KARL STORZ D-Light C PDD Flexible Videoscope System in detection of bladder cancer in patients with bladder cancer.
Protocol number: PC B308/13 Blue Light Flexible Cystoscopy with Cysview Study
Number of patients/sites planned: Approximately 360 patients are planned to be included in the study. Enrolment will continue until 100 patients have received repetitive Cysview instillations in the study. Approximately 15 sites in the US will participate.
Phase of development: 3
Primary objective: To compare blue light cystoscopy with Cysview to white light cystoscopy in the detection of bladder cancer during surveillance cystoscopy. **Secondary objectives**: To assess the efficacy and safety of blue light cystoscopy with Cysview after repetitive use. To compare blue light cystoscopy with Cysview to white light cystoscopy in the detection of carcinoma in situ (CIS).
Study design: This is a prospective, open, comparative within-patient controlled phase 3 multicenter study in patients with bladder cancer. There will be a maximum of three study visits: A screening visit, a surveillance cystoscopic examination and a cystoscopic examination in the operating room (OR) for patients with suspicion of recurrence after the surveillance cystoscopy. In addition there will be a follow-up telephone call for patients undergoing the OR visit within one week after the patient has discussed the pathology report with the study investigator. The first four patients included at each center will be training patients. The training patients will complete the surveillance visit as described below, and then discontinue study participation. Further management will be according to the hospital's clinical routine. For the design of the clinical trial, the comparator is white light cystoscopy. To reduce possible bias in the white light cystoscopic examination, a small number of patients will be randomized to discontinue the study following the white light cystoscopy and before the blue light examination in the surveillance setting.

Malignancy is confirmed by consensus pathology panel read of biopsies taken during the OR examination. The pathology result is obtained from a consensus pathology panel, and the consensus interpretation will be considered the standard of truth for all efficacy endpoints. Malignany will be pathology diagnosis of PUNLMP, CIS, Ta, T1 or T2-T4.

Screening visit
If feasible, the screening visit may be combined with the surveillance visit. Patients may be consented for the study before the screeing visit. The patient will be asked questions about patient reported outcomes

Surveillance visit:
Prior to the examination, the patient's assessment of bladder function will be recorded. All patients will receive an instillation of 50 mL Cysview 8 mM solution, which must be retained for minimum one and no more than 3 hours before the cystoscopy. After bladder evacuation, rinsing and filling of the bladder with cystoscopic irrigation fluid, a standard white light cystoscopy using the KARL STORZ D-Light C PDD Flexible Videoscope System will be done. Suspected malignant lesions will be counted and evaluated.
After the white light examination, an envelope with the patient's randomization allocation will be opened. Patients randomized to terminate the study will be treated according to clinical practice. The other patients will be examined with the investigational PDD Flexible Videoscope System using blue light. Lesions suspected to be malignant seen with blue light will be counted and evaluated. To assess possible effects on the bladder endothelium of repetitive use of Cysview, non-malignant mucosal abnormalities will be assessed using white and blue light. The training patients will not be part of the randomization, but will be examined with both white and blue light. Patients undergoing blue light examination will again be asked questions about patient reported outcomes. The investigator will be asked if the findings under blue light would have caused any change in patient management in the investigator's normal clinical practice.

Operating room visit:
Upon suspicion of recurrence in the surveillance examination, the patient will be referred to further examinations and treatment in the OR. The patient's assessment of bladder function will be recorded for all patients prior to the Cysview instillation. A 50 mL Cysview 8 mM solution will be instilled between one and 3 hours before the examination.
Cystoscopy will then be performed in the OR with anesthesia control, using the approved KARL STORZ D-Light C PDD System with rigid cystoscope. The bladder will first be examined under white light, and all lesions will be mapped. Cystoscopy will continue under blue light, and all lesions detected under blue light will be mapped. Mucosal abnormalities will be assessed using white and blue light, and all lesions seen with white and/or blue light will be biopsied. A transurethral resection or cold-cup removal of all identified lesions will be done according to standard clinical practice, utilizing both white light and blue light. Tissue from biopsies will be collected for histological evaluations. The local pathologist will evaluate biopsied tissue for clinical pathological evaluations as part of clinical practice before the slides are sent for consensus pathology panel read.

Telephone follow-up:
A final collection of bladder function assessment and patient reported outcomes will be done by phone within one week after the patient has discussed the pathology results with the study investigator.

Visit flow chart (main efficacy and safety assessments):

Visit 1: Screening
May be combined with Visit 2
Screening procedures
Patient reported outcomes

Visit 2: Surveillance
Within 4 weeks of Visit 1
Urine cytology
Patient's assessment of own bladder function
Cysview administration procedure
WL flex. cystoscopy and lesion evaluation
Randomization → If randomized to termination:
Record AEs and mucosal abnorm.
Terminate study participation,
treatment according to normal routine
BL flex. cystoscopy and lesion evaluationMucosal abnormality assessment
Patient management assessment
Patient reported outcomes
Record AEs

If suspicion of recurrence ↓

If training patient or no suspicion of recurrence:
Terminate study participation,
treatment according to normal routine

Visit 3: Operating room
Within 6 weeks of Visit 2
Patient's assessment of own bladder function
Cysview administration procedure
WL rigid cystoscopy and lesion mapping
BL rigid cystoscopy and lesion mapping
Mucosal abnormality assessment
Biopsy/TURB
Record AEs

Visit 4: Telephone follow-up
Within one week after patient has received pathology results
Patient's assessment of own bladder function
Patient reported outcomes

WL = white light
BL = blue light
flex. cystoscopy = cystoscopy with investigational PDD Flexible Videoscope System
rigid cystoscopy = cystoscopy with approved rigid PDD System

Inclusion criteria:

1. Patients with bladder cancer in follow-up for tumor recurrence (Note: Patients must be included only at the first surveillance cystoscopy after a histologically confirmed tumor. The histologically confirmed tumor could either be from a TURB or from a surveillance cystoscopy where a biopsy was taken and a tumor was confirmed by histology)
2. History of one or more of the following:
   - Multiple tumors
   - Recurrent tumors
   - High grade tumor(s)
3. Age 18 or older
4. Written informed consent signed

Exclusion criteria:

1. Gross haematuria. (Note: Gross haematuria is defined as a heavy bladder bleed resulting in significant 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 haematuria limitations to cystoscopy)
2. Patients who cannot undergo in-office or operating room cystoscopy (Note: Training patients are eligible even if they cannot undergo operating room cystoscopy)
3. Patients who have received BCG immunotherapy or intravesical chemotherapy within the past 6 weeks prior to the procedure
4. Porphyria
5. Known allergy to hexaminolevulinate hydrochloride or a similar compound
6. Pregnancy or breast-feeding (all women of child-bearing potential must document a negative urine pregnancy test before study inclusion and use adequate contraception during the study
7. Participation in other clinical studies with investigational drugs either concurrently or within the last 30 days
8. 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
9. Patients that the investigator believes are unlikely to comply with the protocol, e.g. mental condition rendering the patient unable to understand the nature, scope, and possible consequences of participating in the clinical study, uncooperative attitude or unlikelihood of completing the study

Key dates:

Start of recruitment: 3Q 2015
End of recruitment: 3Q 2016
Last study visit: 4Q 2016

Endpoints:

Endpoints for comparing blue light cystoscopy with Cysview to white light cystoscopy (surveillance examination):

Primary efficacy endpoint:

- Proportion of patients with histologically confirmed malignancy where malignancy is only detected with blue light cystoscopy with Cysview and not white light cystoscopy

Secondary efficacy endpoints:

- Proportion of patients with false positive lesion(s) detected only with blue light cystoscopy with Cysview and no lesions detected with white light
- Proportion of patients with additional findings detected with blue light cystoscopy with Cysview compared to white light

Safety endpoint:
- The proportion of patients with AEs following the surveillance examination

Endpoints for assessment of efficacy and safety of repetitive use of blue light cystoscopy with Cysview (examination in OR):
Secondary efficacy endpoints:
- Proportion of patients where one or more additional malignant lesions were detected with blue light cystoscopy with Cysview compared to white light
- Lesion detection rate for blue light cystoscopy with Cysview and for white light cystoscopy per lesion type (PUNLMP, CIS, Ta, T1, T2-4)
- Proportion of false positive lesions seen with blue light cystoscopy with Cysview compared to white light cystoscopy

Safety endpoints:
- Proportion of patients with adverse events considered causally related to Cysview and/or blue light in the surveillance examination compared with the OR examination
- Proportion of patients with a worsening in bladder function as assessed on the bladder evaluation form (UDI-6) from surveillance to the OR visit and from the OR visit to the one-week follow-up
- Proportion of patients with apparent inflammatory and/or fibrotic changes in the surveillance cystoscopic examination compared to the to the OR cystoscopic examination

Endpoint for comparing blue light cystoscopy with Cysview to white light cystoscopy in the detection of CIS (examination in OR):
Secondary efficacy endpoint:
- Proportion of patients with one or more CIS lesions detected with blue light cystoscopy with Cysview and none with white light cystoscopy

Efficacy and safety variables and assessments:

Efficacy assessments:
All suspicious lesions will be biopsied in the OR examination. All biopsies will be histologically verified by consensus panel pathology to reduce the variability of the pathology diagnosis used in the efficacy analyses. The 1998 World Health Organization/International Society of Urologic Pathology consensus classification and the 2002 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 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 sit together at a multi-headed

microscope. 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 PUNLMP, CIS, Ta, T1 or T2-T4 by the consensus panel. The consensus panel result will be used for assessment of the efficacy endpoints.
For the secondary efficacy endpoint comparing blue light cystoscopy with Cysview to white light in surveillance, “additional findings” are defined as fulfilling one of the following criteria:

	WL:	**BL:**
I	0	≥1 lesion seen
II	1-4*	# of lesions seen with BL> # lesions seen with WL or at least one of the lesions seen with BL > 0.5 cm
III	Low grade**	High grade**

*Patient has a history of low grade bladder cancer, and all lesions seen in WL are ≤ 0.5 cm
**Based on previous disease history. High grade disease suspicion after BL must be confirmed histologically in the OR examination

For this endpoint, the number of lesions will be based on lesion count. Only patients with at least one histologically confirmed malignancy from the biopsy obtained in the OR examination will be included in the analysis of this endpoint. Confirmed malignancy will be evaluated on patient level, not per lesion.

The investigator will be asked questions on how the patient would have been managed in his/her normal clinical practice based on the findings under blue light examination compared to the white light examination during surveillance cystoscopy.

The question relates to what the investigator would normally do in his/her clinical practice, as the study requires that all patients with suspicious findings are sent to the OR.

Safety assessments:
Safety data will be recorded for all patients, including training patients and patients randomized to discontinue the study. The adverse events’ causal relationship to Cysview and/or blue light will be assessed by the performing clinical investigator urologist.

Additional safety data will be collected to assess possible effects on the bladder endothelium of repetitive use of Cysview. The data will not be registered as adverse events. Non-malignant mucosal abnormalities identified during the cystoscopic examination in both surveillance setting and OR will be assessed for size and category (inflammation, fibrosis, scar, other).

All patients will provide a bladder function assessment by the questions on the UDI-6 form prior to the surveillance examination (baseline), prior to the examination in the OR and after the OR visit.

Patient reported outcomes:
Patient reported outcomes will be collected on the screening, surveillance and telephone follow-up visits to capture changes in patients level of anxiety, pain and experience with blue light cystoscopy procedure.

Populations and sample size:

Populations:
The population for comparing the efficacy of blue light cystoscopy with Cysview to white light cystoscopy in surveillance is all patients enrolled in the study who underwent surveillance cystoscopy and were found to have histologically confirmed malignancy. This is also the population for assessing the proportion of patients where additional findings are detected with blue light cystoscopy with Cysview compared to white light. The population for assessing the safety of blue light cystoscopy with Cysview in surveillance is all patients who received a Cysview instillation in the surveillance setting, including training patients and patients randomized to discontinue the study.

The repetitive use efficacy population is all patients with with histologically confirmed malignancy. The repetitive use safety population is all patients who received a Cysview instillation for both the surveillance and OR examinations.

The CIS efficacy population is all patients with histologically confirmed CIS who underwent the OR examination.

Determination of sample size:
The primary endpoint is the proportion of patients with histologically confirmed malignancy where malignancy is only detected with blue light cystoscopy with Cysview in surveillance (P). Superiority of blue light cystoscopy with Cysview will require that the lower 97.5% confidence limit for P exceeds 0.5% (null hypothesis). Under the assumption that P (alternative hypothesis) is 9% and a power of 90%, a total of 42 patients with histologically confirmed malignancy is needed.

To ensure sufficient data to assess safety of repetitive use, a larger number of patients is required. The study will be sized to provide an estimate of the related adverse event rate that is sufficiently ‘precise’ to rule out a clinically important upper bound. The related adverse event rate following a single administration of Cysview was 7.8% in a pivotal phase III study, and the rate is not expected to increase with repeat administrations.15% is considered to be a clinically acceptable upper bound on the related adverse event rate to determine that patients who receive more than one instillation of Cysview and blue light cystoscopy do not experience clinical significantly more related events than after one such procedure. For this purpose, 100 patients are needed with repeated administration of Cysview.

Based on epidemiologic data it is assumed that 35% of the patients examined in the surveillance setting will have lesions seen with white and/or blue light and be referred to the OR for a second Cysview instillation and examination. Including four training patients at each site and a small number of patients who will be randomized to terminate the study during the surveillance examination, approximately 360 patients must be enrolled in the study to get 100 patients with repeated administration of Cysview.

Statistical methods and planned analyses:

Efficacy and safety of blue light cystoscopy with Cysview in surveillance:
The efficacy and safety evaluations will be based on data collected in the surveillance examination, and confirmatory biopsies from the OR examination.

Efficacy analyses:
The intent of the primary efficacy endpoint analysis is to show that malignancy is detected with blue light cystoscopy with Cysview in the surveillance setting in cases where no malignancy is observed with white light. This will be the group of patients where at least one lesion is seen with blue light and none with white light, and where malignancy is confirmed histologically in the OR examination.

The primary efficacy endpoint will be analyzed using an exact one-tailed test for a single proportion based on the cumulative binomial distribution with a significance level of 2.5%. The following hypothesis will be tested:

Null hypothesis: H_0: $P \leq 0.005$ (0.5%)
Alternative hypothesis: H_1: $P > 0.005$ (0.5%)

The lower limit of the 97.5% confidence interval for the observed proportion will be constructed using exact binomial methods (Wilson scores).

The false detection rate addresses the concern for patients who have an intervention unnecessarily due to false positive lesions seen with blue light only. A patient with false positive lesions attributable to blue light only is defined as having one or more lesions seen with blue light and no lesions seen with white light in the surveillance setting, but with no histologically confirmed malignancy from the OR examination. The proportion of patients with false positive lesions will be calculated among all patients with suspected lesions in the surveillance setting, i.e. all patients where a lesion was seen with white light and/or Cysview blue light. This is the group of patients who, in clinical practice, will either have the lesions removed in the surveillance setting or referred to the OR for further examination and treatment, and is therefore the relevant denominator. For comparison, the corresponding white light false detection rate will also be calculated; patients with false positive lesions attributable to white light only are those who have one or more lesions seen with white light and no lesions seen with blue light, and no histologically confirmed malignancy from the OR examination. The denominator for this proportion is the same as for the blue light false positive rate.

The assessment of additional findings will be evaluated by calculating exact two-sided 95% one-sample confidence limits for the estimated proportion.

The investigators' assessment of change in patient management based on the findings in blue light cystoscopy with Cysview compared to white light cystoscopy will be summarized descriptively.
Safety analysis:
The proportion of patients with AEs following the surveillance examination will be calculated.

Efficacy and safety of repetitive use:
Efficacy analyses:

The efficacy analysis of repetitive use will be based on data collected in the OR examination.

Lesions with a pathology diagnosis from the central pathology read of PUNLMP, CIS, Ta, T1 or T2-T4 will be considered malignant.

The proportion of patients who have one or more additional PUNLMP, CIS, Ta, T1, T2-T4 lesions detected with blue light cystoscopy with Cysview compared to white light cystoscopy will be evaluated by calculating exact two-sided 95% one-sample confidence limits for the estimated proportion.

The lesion detection rate for white light and blue light per lesion type will be calculated on a lesion level as the total number of lesions of a specific type that were detected with blue light divided by the total number of lesions of the same type that were detected with either blue or white light, or both. This will be done as one rate over all patients. The corresponding detection rates for white light cystoscopy will be calculated. Proportions and exact 95% confidence intervals will be calculated by lesion type.

A false positive lesion is defined as suspected lesion histologically confirmed not to be one of the following: PUNLMP, CIS, Ta, T1, T2-T4. The false positive detection rate for blue light cystoscopy with Cysview is calculated as the total number of false positive lesions divided by the total number of lesions seen with blue light. The false positive detection rate for white light cystoscopy will be calculated in the same way. Proportions and exact 95% confidence intervals will be calculated for white light and blue light cystoscopy.

<u>Safety analysis:</u>
Since these groups are not randomized, it is not statistically valid to apply a formal hypothesis test to compare the rates, so the analysis of safety data will be descriptive in nature.

The frequency and severity of adverse events considered causally related to administration of Cysview and/or blue light exposure and the proportion of patients with related adverse events will be summarized and compared for the surveillance examination and the OR examination.

All AEs will be evaluated by

- number of prior exposures to Cysview and blue light
- timing in relation to the most recent exposure
- repetition of the same AE within a patient following repeated exposure and
- change in severity of a repetitive AE following repeated exposure

UDI-6 scores will be summarized descriptively and compared for the surveillance examination, OR examination and the follow-up assessment.

The proportion of patients with apparent inflammatory and/or fibrotic changes visually assessed during each cystoscopic examination will be calculated.

Efficacy in the detection of CIS:
The efficacy analysis of detection of CIS will be based on data collected in the OR examination.

The proportion of patients with one or more CIS lesions detected with blue light and none with white light will be evaluated using an exact binomial test for a single proportion with a significance level of 2.5% (one-sided) to evaluate the following hypothesis:

Null hypothesis: H_0: $\pi \leq 0.001$ (0.1%)
Alternative hypothesis: H_1: $\pi > 0.001$ (0.1%)

Exact one-sided 97.5% confidence limits will be calculated for the estimated proportion.

Patient reported outcomes:
Data from patient reported outcomes will be summarized descriptively for screening examination, surveillance examination and the follow-up assessment.