2. SYNOPSIS

Name of Sponsor: Photocure ASA	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Hexvix®		
Name of Active Ingredient: Hexaminolevulinate		

Title of study: An open, prospective, within-patient, controlled, multi-centre Phase 2a study of Hexvix flexible fluorescence cystoscopy and white light flexible cystoscopy in the detection of bladder cancer after 30 minutes intravesical instillation of Hexvix® (hexaminolevulinate) in patients with known or suspected bladder cancer

Coordinating Investigator: [redacted]

Study centres: This study was conducted in 4 centres in Germany.

Publications (reference): None at the time of writing this report.

Studied period (years): Date study started: 13 December 2011 (FPFV) Date study completed: 24 May 2012 (LPLV)	**Phase of development:** 2a

Objectives:

Primary Objective

- To compare Hexvix flexible cystoscopy and white light flexible cystoscopy in the detection of histologically confirmed bladder tumour lesions defined as dysplasia; carcinoma in situ (CIS); Ta; T1; and ≥T2 after 30 minutes intravesical instillation of Hexvix.

Secondary Objectives

- To compare the detection rates of histologically confirmed bladder tumour lesions, defined as dysplasia; CIS; Ta; T1; and ≥T2 after 30 minutes intravesical instillation of Hexvix.
- To compare the proportion of false positive lesions of Hexvix flexible cystoscopy and white light flexible cystoscopy after 30 minutes intravesical instillation of Hexvix.
- To assess the overall fluorescence per patient for lesions seen under blue light after 30 minutes intravesical instillation of Hexvix.

Methodology: This was an open, Phase 2a, prospective, multi-centre within-patient, controlled study of intravesical Hexvix in patients with bladder cancer.

Patients with multiple bladder tumours, defined as ≥2 lesions, based on an outpatient cystoscopy, were eligible for inclusion in this trial. Potentially eligible patients were informed, both verbally and in writing, about the study. If the patient agreed to participate in the study, they signed an informed consent form before any procedures required in the protocol were performed. A total of 34 evaluable patients were to be enrolled. After informed consent was given, all patients were checked for eligibility against the inclusion and exclusion criteria.

All patients received a single 50 mL intravesical instillation of 8 mM Hexvix. Thirty minutes after the start of Hexvix instillation, the bladder was evacuated and patients underwent white light flexible cystoscopy (KARL STORZ), followed by Hexvix blue light flexible cystoscopy, standard rigid cystoscopy and TURB.

The patients were followed until discharge or for a maximum of 24 hours to record adverse events and concomitant medications or procedures.

Number of patients (planned and analysed):

It was planned that enrolment would continue until 34 patients with histologically confirmed tumours

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were enrolled. Thirty-eight patients were enrolled, received Hexvix and were treated according to the protocol. Of these, only 31 had histologically confirmed tumours. In the ITT and PP population the 31 patients with histologically confirmed tumours were included as well as the seven patients without, due to a misinterpretation of the definition of the ITT and PP populations. This error had no effect on the final outcome of the study overall. All 38 patients were included in the safety analysis. The study was stopped prematurely due to lack of efficacy in the 31 patients.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

The patients were indicated for a transurethral resection of the bladder (TURB) based on an outpatient cystoscopy and fulfilled the following inclusion criteria:

- Multiple bladder tumours, defined as ≥2 lesions, based on an outpatient cystoscopy.
- Known urinary urge symptoms or problems or pain holding back urine for longer than 30 minutes.
- Age 18 years or above.

***Exclusion Criteria*:**

Patients were excluded from participating in this study if they met any of the following criteria:

- Known tumours in the prostatic urethra or distal urethra.
- Gross haematuria.
- Porphyria.
- Hypersensitivity to the active substance or to any of the excipients of the solvent.
- Participation in other clinical studies with investigational drugs either concurrently or within the previous 30 days.
- Women of child-bearing potential.
- Treatment with BCG or chemotherapy within 3 months prior to study inclusion.
- Conditions associated with a risk of poor protocol compliance.
- Patient was the investigator or any sub investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
- Mental condition rendering the patient unable to understand the nature, scope, and possible consequences of the clinical study.
- Unlikely to comply with the protocol.

Test product, dose and mode of administration, batch numbers:

Hexvix 8 mM solution. 50 mL intravesical solution containing 85 mg of hexaminolevulinate. The solution was retained in the bladder for 30 minutes, followed by flexible cystoscopy under white and blue light. Hexvix was sourced from local pharmacies, therefore several batches were used.

Duration of treatment: Single dose. The solution was retained in the bladder for 30 minutes.

Reference therapy, dose and mode of administration, batch numbers:

Flexible cystoscopy under white light without prior treatment.

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Criteria for evaluation:

Primary endpoint:

The proportion of patients with additional histologically-confirmed lesions defined as one of the following: dysplasia; CIS; Ta; T1; ≥T2; papillary urothelial neoplasms of low malignant potential (PUNLMP); and grade only demonstrated with Hexvix flexible cystoscopy but not with white light flexible cystoscopy after 30 minutes intravesical instillation of Hexvix. The analysis of PUNLMP and grade only was a change to the planned analysis.

Secondary endpoints:

The detection rates of Hexvix flexible cystoscopy and white light flexible cystoscopy for all biopsies overall and for each of the following histological results: dysplasia; CIS; Ta; T1; ≥T2; PUNLMP; and grade only after 30 minutes intravesical instillation of Hexvix. The analysis of PUNLMP and grade only was a change to the planned analysis.

The proportion of false positive lesions of Hexvix cystoscopy and white light cystoscopy after 30 minutes intravesical instillation of Hexvix.

The proportion of patients with different fluorescence assessment scores for lesions seen under blue light flexible cystoscopy after 30 minutes intravesical instillation of Hexvix.

Safety endpoint:

The proportion of patients with drug related adverse events (adverse drug reactions, ADRs).

Statistical methods:

The primary endpoint was analysed using an exact test for a single proportion based on the cumulative binomial distribution with the significance level of 2.5% (one-sided) to determine if the proportion was significantly greater than a hypothesized value of 1.0%. An exact one-sided 95% one-sample confidence interval (CI) was calculated for the estimated proportion. Proportions, testing, and exact 95% CIs were also calculated by lesion type (dysplasia, CIS, Ta, T1, ≥T2, PUNLMP, and grade only).

Secondary endpoints (detection rates, false detection rates) were calculated on a biopsy level and presented with exact 95% CIs based on the binomial distribution. Fluorescence scores were presented with the corresponding exact 95% CIs based on the binomial distribution.

Safety analysis was descriptive. Continuous variables were summarised by the number of patients with non-missing data, mean, standard deviation (SD), median, minimum and maximum values. Discrete variables were summarised by their counts and associated percentages.

Exploratory analyses could have been carried out for selected subgroups of interest. Unless mentioned otherwise, CIs were one-sided and had 95% coverage probability.

SUMMARY – CONCLUSIONS

Thirty-eight patients were included in the study, 31 (81.6%) of whom had histologically-confirmed tumours. Most patients (81.6%) were male. The mean age was 68.9 years (range 38 to 83 years), mean weight was 83.7 kg and mean height was 174.3 cm.

Efficacy Results

Primary Efficacy Variable

- Of 31 patients in the intent-to-treat (ITT) population with at least one positive lesion detected

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with either white light or blue light, one patient (3.2%) had positive lesions detected with blue light but not with white light. The proportion of patients with additional histologically confirmed lesions under blue light was not significantly greater than 1.0% (p=0.2677). The additional lesions detected in this patient represented 1/10 cases of dysplasia (10.0%) and 1/5 cases of CIS (20.0%). The proportions of patients with additional cases detected were not significantly greater than 1.0% for dysplasia (p=0.0956) but were significantly greater than 1.0% for CIS (p=0.0490). Given the small number of patients with CIS, the associated results should be interpreted with caution.

Secondary Endpoints

102 lesions were detected overall, of which 70 (68.6%, 95% CI:58.7, 77.5) were detected in blue light, and 100 (98.0%, 95% CI:93.1, 99.8) were detected with white light. Higher lesion detection rates for white versus blue light were observed for dysplasia (96.4% (95% CI:81.7, 99.9) versus 57.1% (95% CI:37.2, 75.5), respectively), Ta (100.0% (95% CI:93.6, 100.0) versus 73.2% (95% CI:59.7, 84.2) respectively), T1 (100.0% (95% CI:54.1, 100.0) versus 66.7% (95% CI:22.3, 95.7) respectively), and PUNLMP (100.0% (95% CI:47.8, 100.0) versus 60.0% (95% CI:14.7, 94.7) respectively). Lesion detection rates were the same for blue and white light for lesions classified as CIS (83.3%) and by grade only (100.0%).

The false detection rate (ITT population including patients without histologically confirmed tumours) was higher for blue light (33.3%, exact 95% CI: 24.4%, 43.2%), than for white light (28.6%, exact 95% CI: 21.3%, 36.8%).

Hexvix fluorescence seen under blue light was none in seven patients (18.4%), poor in 20 patients (52.6%), medium in seven patients (18.4%), and good in four patients (10.5%) (ITT population including patients without histologically confirmed tumours). If the seven patients without lesions are excluded from the analysis (ITT/PP populations) the fluorescence intensity is none in five patients (16.1%), poor in 19 patients (61.3%), medium in four patients (12.9%), and good in three patients (9.7%).

Safety Results

There were no patients with treatment-related adverse events, death, serious adverse events, treatment interruptions or discontinuations in this study.

There were no patients with clinically meaningful changes in vital signs from before to after cystoscopy, and no patients had changes in physical examination findings from before to after cystoscopy.

Conclusions

- Instillation and retention of Hexvix for 30 minutes before start of cystoscopy (white light followed by blue light) does not provide sufficient fluorescence to enable consistent detection of malignant lesions under blue light cystoscopy. However, as has been demonstrated in some patients in the previous 305 study, sufficient fluorescence seems to be built up in patients who cannot hold Hexvix for the recommended time, as long as the time from instillation to cystoscopic examination is at least one hour.

Date of the report: 9 April 2013