2 SYNOPSIS

Sponsor: Photocure ASA, Hoffsveien 4, 0275 Oslo, Norway. Phone: +47 22 06 22 10. Telefax: +47 22 06 22 18	**Individual study table referring to part of the dossier** Volume: Page:	**(For National Authority use only)**
Finished product: Hexaminolevulinate (HAL) capsules 100 mg Two formulations: immediate release (A) and sustained release (B)		
Active compound: Hexaminolevulinate (HAL) hydrochloride		
Title of study: An open dose-finding study of oral applied hexaminolevulinate (HAL) imaging in patients with suspicion or high risk of neoplasia in the colon		
[redacted]		
Study Centres: Centre 1: Department of Medicine II, Munich Hospital Pasing, Germany. Academic Teaching Hospital of Ludwig-Maximilians-University, Munich, Germany. Centre 2: Hospital Martha-Maria, Stadenstr. 58, 90491 Nuernberg, Germany. Centre 3: Department Internal Medicine I, University Hospital, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany		
Publication (reference) Not applicable		
Study period: FEB 2009 – OCT 2009 (date of first enrolment): 18 FEB 2009 (date of last completed): 22 OCT 2009	**Phase of development:** Phase I/II	
Objectives: *Primary objective:* To determine carcinoma and adenoma lesion true positive detection rate of HAL fluorescence colonoscopy in patients with known or strong suspicion of neoplasia (carcinomas or adenomas) of the colon. *Secondary objectives:* To determine carcinoma and adenoma lesion false positive detection rate of HAL fluorescence colonoscopy. To compare carcinoma and adenoma lesion true positive detection rates and the false positive detection rates of fluorescence and standard (white light) colonoscopy. To further characterise the safety profile of HAL fluorescence colonoscopy		
Methodology: This was an open, dose-finding study of HAL fluorescence colonoscopy investigating the timing and coverage of HAL in the colon. Two phases of the study were planned: a dose-finding phase followed by a fixed dose phase. After standard bowel cleansing 2-4 100 mg HAL capsules (immediate release formulation (A) or sustained release formulation (B)) were administered 6 or 7 hours prior to colonoscopy. 500 ml Delcoprep was given 45 minutes post capsule ingestion. Colonoscopy was performed with a flexible videoendoscope capable of presenting standard white light images of lesions as well as red fluorescence images when the lesions are illuminated by blue light. Colon inspection was performed by segments (Caecum and C. ascending, right flexura and C. transverse, left flexura and C. descending, sigma and rectum), first in standard white light, then in blue light (fluorescence). All suspected lesions in blue and white light were biopsied or resected to obtain tissue material for histology. In addition non-suspicious mucosa in blue and white light was biopsied (2x2 biopsies from two locations).The following HAL administration regimes were evaluated in a total of 13 patients during the dose-finding part of the study: 200mg/6h/formulation A, 200mg/6h/formulation B, 300mg/7h/formulation A, 300mg/7h/formulation B and 400mg/6h/formulation A. These 5 regimes were chosen based on a predefined titration scheme.		

Number of patients:
Planned: Three (3) patients were planned to be included in each dose regime of the dose-finding part of the study and 32 patients were planned to participate in the fixed dose phase.
Analysed: Thirteen (13) patients were included in the study. The study was stopped due to inadequate efficacy after 13 patients were evaluated. The findings that resulted in study termination are described in the Efficacy results section below.

Diagnosis and main criteria for inclusion:
Inclusion criteria:
1. Female and male subjects with known or strong suspicion of adenoma or carcinoma of the colon after screening or follow-up colonoscopy.
2. Female and male patients with verified neoplastic lesions.
3. Written Informed Consent obtained
4. Age 18 years or above

Exclusion criteria:
1. Known or suspected Porphyria
2. Contraindications to colonoscopy
3. Known allergy to hexaminolevulinate, methyl aminolevulinate or aminolevulinate or a similar compound
4. Participation in other clinical studies either concurrently or within the last 30 days
5. Female subjects with childbearing potential (i.e. ovulation, pre-menopausal, not surgically sterile) not willing to use a medically accepted contraceptive regimen while on treatment.
6. Patients with ALAT/ASAT >2ULN and calculated GFR<50ml/min/1,73m2
7. Pregnant or lactating women
8. Conditions associated with a risk of poor protocol compliance
9. Vulnerable patients

Investigational product, dose and mode of administration, batch number:
Investigational drug: HAL capsules 100 mg, oral administration as a single 200-400 mg dose, batch number VG2500/CT2577 (formulation A) and VG2498/CT2577 (formulation B).
Device: A flexible videoendosope-equipment for photodynamic diagnosis model PDD-coloscope 13904 X PKS (KARL STORZ)

Duration of procedure: Investigational drug was administered 6 or 7 hours prior to endoscopy. The patients were followed for one week after the colonoscopy for safety.

Reference therapy, dose and mode of administration, batch number:
NA

Criteria for evaluation:
Efficacy:
The detection of adenomas and carcinomas in both blue and white light were the main efficacy criteria. Based on the histology, lesion true and false detection rates were calculated.

Safety:
Adverse events, vital signs (heart rate and blood pressure), haematology (haemoglobin, white blood cells and platelets), clinical chemistry (bilirubin, alkaline phosphatase (ALP), ALAT, ASAT, creatinine and albumin) were evaluated during the course of the study.

Statistical methods:
Determination of sample size: The lesion true positive detection rate for carcinoma and adenoma lesions (calculated as a percentage of lesions seen and classified as carcinomas or adenomas) was used as the basis for sample size justifications. Under the requirement that the estimate would fall within 10% of its expected mean (i.e. a confidence interval of length 20%), a sample size of 100 lesions was needed. Assuming an average of at least 3.15 carcinoma or adenoma lesions per patient (based on results from a previous study) at least 32 patients in the final dose group was needed.

Statistical evaluation of the study variables:
Lesion true positive and false positive detection rates were calculated for both white and blue light observations. Tables of the efficacy assessments were provided for each combination of HAL dose and type of release. No formal statistical testing was conducted, but 95% confidence intervals of the rates were provided for the results by HAL dose and type of release subgroup for white and blue light.

Safety assessments were presented for the subgroups and for all patients together.
Continuous data were presented with their mean, standard deviation, minimum and maximum, together with the number of patients these values represented. Discrete data were presented using counts and rates. Some tables used lesion as the counting unit. Results were presented using SAS version 9.2.
Data sets analyzed: The all patients treated population (APT) of the present study included all patients who received HAL (n=13). This population was used for evaluation of the safety data. The per-protocol population (PP) included all patients who completed the study without major protocol violations. The PP population was used in the analysis of the primary and secondary efficacy variables. In the present study, the APT population was identical to PP population.
The main efficacy objective of the study was the true positive detection rate of adenomas and carcinomas using HAL fluorescence colonoscopy. The efficacy analysis was performed on pooled lesion data collected instead of on a per-patient basis.
Individual data could be excluded from analyses if it could endanger the scientific aspects of the study. This was done in one instance. One adenoma was seen among the randomly collected tissue samples. After discussions it was decided not to include this in the PP analysis of true positive detection rates as it was not considered a lesion since it was not seen in white or blue light. This lesion was included in the Intention-to-treat (ITT) population analysis of true detection rates.

Patients' disposition and characteristics: Thirteen patients were included into the study. All of them completed the study. The table below summarizes the different treatment groups and the patient population:

Administration regime	Number of patients	Age (yrs)	Sex (f/m)
200 mg, 6 h, formulation A	2	70.0±2.8	1/1
200 mg, 6 h, formulation B	2	64.5±4.9	0/2
300 mg, 7 h, formulation A	3	69.0±3.6	0/3
300 mg, 7 h, formulation B	3	55.3±1.5	1/2
400 mg, 6 h, formulation A	3	70.3±2.5	2/1
All	13	65.6±6.7	4/9

Efficacy results: The main efficacy criterion of the study was the detection rate of adenoma and carcinoma lesions using blue and white light. True detection rate was determined on pooled data on lesions from all 13 patients. Seventy-six (76) biopsy samples were collected during the colonoscopy procedures and 43 of them were found to be adenomas. No carcinomas were observed. Fifty-four (54) biopsies were taken from suspected areas. Fifty-two (52) of them were confirmed histologically to be abnormal. Among them were 42 adenomas.
As described above, under 'Data sets analyzed' section, it was decided not to include one of the adenoma detected among the random biopsies in the PP analysis of true detection rates as it was not considered a lesion (not seen in neither white nor blue light). The sample was included in the ITT analysis of true detection rates. Descriptive data on lesion histology, type and fluorescence were based on all 76 biopsy samples.
PP analysis showed that while the true positive detection rate for white and blue light colonoscopy was 100% it was 97.6% for white light only. The true positive detection rate of blue light only was 16.7%, however dosage groups 300mg of formulation B and 400mg of formulation A showed an indication of higher detection rates of 37.5% and 33.3%, respectively.
All in all, blue light colonoscopy did not contribute in a significant extent to an increase in the white light detection rate, since most of the samples detected in blue light were also detected in white light. Of the 42 adenomas 41 were observed with white light, and only 1 was seen in blue, but not in white light – hence the contribution of blue light was 1/42 i.e. 2.4%.
For the true positive detection rate analysis in ITT group the detection rate for white and blue light colonoscopy was 97.7% (42 out of 43 adenomas) versus 95.4% for white light only (41 out of 43 adenomas). Hence, the addition of blue light resulted in an improvement of detection rate of 2.3%.
Examination of the detection rate of non-adenoma lesions (false positive detection rate) showed that 6

out of 33 lesions (18.2%) representing non-adenomatous mucosa were detected with blue light whereas 9 out of 33 lesions (27.3%) were detected with white light and the combined false detection rate was 36.4% (12 lesions).
When evaluating the false positive detection rate by using the number of all lesions identified by white or white and blue light and the number of lesions among them that were not adenomas the values were 18.0% (9 out of 50 lesions) and 22.2% (12 out of 54 lesions) for white light and blue combined with white light, respectively.
The mean fluorescence intensity of the adenomas detected with blue light was 2.4±0.6 for all treatments, increasing from 2.1±0.5 for 300mg dose to 2.7±0.6 for 400mg dose.
Although lesions were found in all parts of the colon most of the lesions detected with blue light were detected in sigma/rectum and caecum/c.ascending. A trend indicating that formulation A might be more efficient in detecting lesions in the early/mid segments of the colon and formulation B in the late segments was observed. The fluorescence intensity of the lesions was independent of the localisation of the lesions within the colon.

Safety results: A total of 5 AEs were registered by 5 patients (38%) during the study. All of the reported AEs were only a single occurrence.
The majority of the AEs were reported as mild. Only one AE was characterized as severe (Large intestine perforation), this AE was also the only AE reported as serious, however not related to study drug.
Two patients experienced AEs that were evaluated by the Investigators to have an uncertain relationship with the investigational product, i.e. 1 case of increased blood bilirubin and 1 case of dermatitis allergic. The allergic dermatitis on the face and upper chest occurred 3.5 days after HAL administration. The patient was allergic to penicillin.
All AEs resolved by the end of the study. No patients were withdrawn from the study due to AEs.
One clinical laboratory value was characterised as abnormal with clinical relevance (increased blood bilirubin), this was reported as AE with uncertain relation to the investigational product.
There were no abnormal vital signs values reported.

Conclusion:
Adequate efficacy for detecting carcinomas and adenomas during colonoscopy with blue light after oral administration of HAL capsules was not achieved and the study was terminated before the fixed-dose part. The detection rate of blue light colonoscopy for all dosage groups combined was 16.7%, reaching 37.5% for the 300mg formulation B dosage group. One explanation for the lack of efficacy could be a premature release of the study drug from the capsule in the gastrointestinal system and an incomplete coverage of HAL in colon.
The present study indicates that oral administration of HAL capsules in this study identified no new safety signals and was well tolerated by patients with known or highly suspected colorectal cancer. However, the formulation of HAL in its current form does not contribute to a sufficient true positive detection rate with blue light due to inadequate coverage of the colon and intensity of fluorescence. Further development of the capsule formulation has to be done to target the release and increase the coverage of HAL in colon.