2 SYNOPSIS

Name of Sponsor: Photocure ASA **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Hexaminolevulinate hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of study: A randomised Phase II dose-finding study of hexaminolevulinate (HAL) photodynamic therapy (PDT) in patients with low/moderate-grade cervical intraepithelial neoplasia (CIN1 or 2)		
Coordinating Investigator: Prof Dr Peter Hillemanns, Department of Obstetrics and Gynecology, Medizinische Hochschule Hannover, Hannover, Germany		
Study centres: This study was conducted in 23 centres: 6 centres in Germany, 8 centres in the Czech Republic, 4 centres in the USA, 3 centres in Slovakia, and 2 centres in Norway.		
Publications (reference): None at the time of writing this report.		
Studied period (years): Date first patient enrolled: 02 June 2011 Date of last patient visit: 23 November 2012	**Phase of development:** II	

Objectives:

Primary Objective:

- To compare patient response rates of three different doses of HAL PDT and placebo at 3 months after one treatment.

Secondary Objectives:

- To compare patient response rates of three different doses of HAL PDT and placebo at 3 and 6 months after last treatment.
- To compare patient response rates of three different doses of HAL PDT and placebo at 9 months after first treatment.
- To compare patient human papilloma virus (HPV) response rates of three different doses of HAL PDT and placebo at 3 and 9 months after one treatment and at 3 and 6 months after last treatment.
- To evaluate patient safety of HAL PDT.

Methodology: This was a Phase II, prospective, randomised, double-blind, placebo-controlled multicentre study. Patients who gave written informed consent were screened for the study. Approximately 240 eligible patients with local pathology of CIN1 or CIN2 were to be randomised in a ratio of 1:1:1:1 to receive one of the following treatments: HAL 5% ointment with illumination, HAL 1% ointment with illumination, HAL 0.2% ointment with illumination or placebo ointment without illumination.

Within 2 months of screening, patients in the HAL PDT groups received HAL ointment vaginally via the Cevira device 5 hours before illumination. Photoactivation was performed with red coherent light (629 nm) at a mean light dose of 100 J/cm^2 for 4.6 hours. Patients in the Placebo group received placebo ointment vaginally via the Cevira device but without the subsequent photoactivation. Response evaluation was performed at 3 months following first and last PDT (based on histology, cytology and HPV status), and at 6 months after last PDT and 9 months after first PDT (based on cytology and HPV status).

All patients were followed up at 1 week and at 3 months after first PDT. Patients with complete response at 3 months after one PDT were followed up at 6 and 9 months after the PDT treatment. All patients recruited in the USA who had CIN2 and who were eligible for conisation at screening underwent surgical excision (LEEP) 3 months after first PDT, irrespective of the response, and then

Name of Sponsor: Photocure ASA **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Hexaminolevulinate hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

terminated the study. All other patients who presented with a non-complete response (ie partial or no response) 3 months after one PDT were to receive a second PDT using the same dose and illumination regimen as for the first treatment. Patients were contacted by telephone by study personnel within 24 hours after administration to ensure correct handling of the device and to assess safety. Three and 6 months after re-PDT, patients attended follow-up visits.

Patients with disease progression or need for immediate treatment according to standard-of-care after one or two PDTs terminated the study and were offered standard-of-care at the investigator's discretion.

Number of patients (planned and analysed): Approximately 240 patients were to be included in this study to ensure a minimum of 176 patients in the primary statistical analysis (44 patients in each of four groups).

A total of 262 patients were treated in the study and included in the intent-to-treat (ITT) analysis set: 65 patients in the HAL 5% group, 67 patients in the HAL 1% group, 62 patients in the HAL 0.2% group, and 68 patients in the Placebo group.

Diagnosis and main criteria for inclusion: Eligible patients were aged 18 years or older, with ectocervical CIN1 or CIN2 as verified by local histology (biopsy) within 2 months prior to study entry. Patients had satisfactory colposcopy examination. Patients also had negative endocervical os by colposcopy, colposcopical visible lesion at Visit 2 (before treatment initiation), and an average sized uterine cervix suitable for application of the Cevira device. All patients gave written informed consent.

Patients were excluded from the study for any reason that could compromise their safety or that could confound the results, including previous treatment of CIN or invasive disease; lesion(s) extending to the vaginal vault, atypical glandular cell carcinoma; suspicion of endocervical disease; or current severe pelvic inflammatory disease, severe cervicitis, or other severe gynaecological infection observed on colposcopy and clinical examination.

Test product, dose and mode of administration, batch numbers: HAL ointment 5% (HAL HCl 100 mg), 1% (HAL HCl 20 mg) or 0.2% (HAL HCl 4 mg) was administered via the Cevira device (Sagentia Ltd., Cambridge, England) followed 5 hours later by red light illumination (629 nm) with a total dose of 100 J/cm^2. The HCl salt is omitted in references to the strength of the ointment throughout this document. The term HAL 5%, 1% and 0.2% ointment is used. However, it is understood that this term describes the strength with reference to the active ingredient HAL HCl.

Batch numbers: HAL ointment 5% K0012A and K1008A, HAL ointment 1% K0011A and K1007A, HAL ointment 0.2% K0013A and K1006A, Cevira device PC002/A, PC002/B and PC002/D.

Duration of treatment: Single dose. A second dose was to be administered to patients with a non-complete response at Month 3.

Reference therapy, dose and mode of administration, batch numbers: Placebo ointment was administered via the Cevira device. The Cevira device did not provide any light in the Placebo group.

Batch numbers: Placebo ointment K0009A.

Name of Sponsor: Photocure ASA **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Hexaminolevulinate hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Criteria for evaluation:

Efficacy parameters:

The analysis of efficacy was based on histology, cytology and HPV status.

The primary endpoint was the percentage of CIN1/2 patients with complete or partial response at 3 months after one treatment. Response was based on central histology review, central HPV and local cytology. Patients with a complete or partial response were defined as responders. Patients with no response or disease progression were defined as non-responders. Complete and partial responses were defined separately for patients with CIN1, CIN1 and HPV negative at baseline, CIN2, and CIN2 and HPV negative at baseline.

The secondary efficacy endpoints were the percentage of patients with complete or partial response at 3 and 6 months after last treatment, the percentage of patients with complete or partial response at 9 months after first treatment, and the percentage of patients with HPV response at 3 and 9 months after one treatment and at 3 and 6 months after last treatment.

A number of exploratory and *post hoc* analyses were also carried out.

Safety:

Safety was evaluated by recording adverse events (AEs), vital signs, laboratory safety parameters, urine pregnancy test results, and concomitant medication use.

Statistical methods:

Analysis of the primary endpoint was based on the Fisher exact test. Point estimates of the responder rates were provided with exact 2-sided 95% confidence intervals (CIs) using the standard method based on the binomial distribution. The secondary response endpoints were analysed using methods similar to the primary endpoint.

Safety parameters were presented descriptively and were summarised by treatment group.

Sub-group analyses were performed for several of the endpoints: patients were split by CIN group and by HPV status at baseline. A number of exploratory analyses were conducted.

SUMMARY

Demographics: Median age overall was 27.0 years (range 18 to 60 years); 258 patients (98.5%) were White.

Efficacy results

Although there was no statistically significant improvement in the overall CIN1/2 population, the study demonstrated a clear dose-response in the CIN2 population with HAL 5% as the preferred dose. At 3 months after first treatment, the proportion of responders in the CIN2 population was 78.9% in the HAL 5% group, 62.1% in the HAL 1% group, 63.2% in the HAL 0.2% group, and 47.6% in the Placebo group. The difference between the HAL 5% and Placebo groups approached statistical significance (p=0.0550). The difference between HAL 5% and Placebo was significant at 3 months after last treatment (p=0.0094), with a response of 94.7% in the HAL 5% group compared to 57.1% in the Placebo group. The dose-response was confirmed in the CIN2 HPV positive population 3 months after last treatment with a statistically significant difference between HAL 5% (92.3%), and placebo (50.0%) (p=0.0200). The HAL 5% response rate was sustainable at 94.7% over 6 months, and maintained a statistically significant difference to the Placebo group (61.9%, p=0.0214).

Clearance of HPV infections is important as HPV drives the development of CIN. In the overall

Name of Sponsor: Photocure ASA **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Hexaminolevulinate hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

CIN1/2 population, the proportion of patients with clearance of baseline HPV infection at 3 months after first and after last treatment was higher in the HAL 5% group (58.1%) compared to placebo (37.5%). The HPV clearance in the HAL 5% (67.7%) and the Placebo (50.0) groups increased compared to 3 months in both groups, maintaining a similar difference at 6 months after last treatment.

The effect on HPV clearance was pronounced in the population with CIN2 at baseline. For these patients, HPV clearance 3 months after last treatment was 61.5% in the HAL 5% group, 37.5% in the HAL 1% group, 41.2% in the HAL 0.2% group and 27.8% in the Placebo group. The clear difference in the proportion of responders between the HAL 5% and Placebo group did not reach significance (p=0.0785) due to the low number of patients in each dose group. The HPV clearance in the CIN2 patients after 6 months was 76.9%, 48.0%, 41.2% and 38.9% respectively. Although there was a clear difference between HAL 5% and Placebo, it again did not reach significance (p=0.0669) due to the small sample size. The results further supported the HAL dose response, HAL 5% being superior.

Of interest was the high clearance of HPV16/18 in patients with CIN2 of 83.3% in the HAL 5% group at both 3 and 6 months compared to 0% and 33.3% in the Placebo group. In the CIN1/2 population, the HPV 16/18 clearance was 53.8% in the HAL 5% group and 11.1% in the Placebo group at 3 months after last treatment, increasing to 61.5% in the HAL 5% group and 33.3% in the Placebo group at 6 months after last treatment. The number of patients with HPV16/18 was small, but suggested a high clearance of the most oncogenic HPV types (HPV16/18), which account for >70% of all cervical cancers.

Re-treatment of patients with a non-complete response 3 months after first treatment showed a possible benefit but this was more pronounced in the CIN1 compared to the CIN2 population.

Histological regression 3 month follow up was sufficient for initial assessment of efficacy in this patient population, but results suggested an increasing HPV clearance compared to placebo at 6 months follow up. The patient response was sustainable throughout the follow-up period of 6 to 9 months.

As the importance of HPV in the development of CIN has become apparent and cytology is regarded as unreliable, a *post hoc* analysis was carried out on the data using a definition of patient response including histology and HPV. For both patients with CIN1 and CIN2 response was defined as absence of CIN2 (at 3 months) and HPV (at 6 months). Using this definition, patients with CIN2 revealed a dose-related response of 84.2% in the HAL 5% group, 48.3% in the HAL 1% group, 42.1% in the HAL 0.2% group and 38.1% in the Placebo group 3 or 6 months after last PDT. This definition of response confirmed the dose response previously documented in the CIN2 population. For patients with CIN1 there was no difference between HAL5% and placebo.

Safety results

HAL PDT was well tolerated by the patients.

One-hundred-and-twenty-five patients reported 261 AEs, but these were mostly mild (85.8%, 224 out of 261 AEs), local and self-limiting.

Ninety-nine patients reported related AEs with vaginal discharge, local discomfort and vaginal spotting being the most common. The number of patients with related AEs was highest in the HAL 5% group (53.8%) compared to the other groups (31.1% to 33.9%), mainly due to a higher number of vaginal discharge and pelvic/abdominal pain events. The events in the HAL 5% group were also on average more severe and of a slightly longer duration.

Vaginal discharge and spotting were generally reported after device removal, while pelvic and abdominal pain was reported during use.

While both vaginal discharge and local discomfort were more commonly reported in the HAL 5%

Name of Sponsor: Photocure ASA **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Hexaminolevulinate hydrochloride	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

group, spotting was reported at a similar level in all groups and probably related to the device rather than drug treatment.

Most AEs were mild or moderate. Six patients each reported one severe AE: two patients in the HAL 5% group (vaginal discharge in both cases), three patients in the HAL 1% group (vaginal discharge, lower abdominal pain, and periorbital cellulitis), and one patient in the HAL 0.2% group (urinary retention). The patient with urinary retention discontinued HAL PDT because of the AE. The event was considered related to the treatment and resolved upon removal of the Cevira device, and the patient recovered and completed the study follow-up.

Three patients had SAEs after removal of the device: salpingo-oophoritis (HAL 5% group), tubo-ovarian abscess (HAL 5% group), and periorbital cellulitis (HAL 1% group). None of the SAEs were considered by the investigators to be related to study treatment, and all of the patients recovered and completed the study. No deaths were reported.There were no signs of significant effects on vital signs including blood pressure, heart rate or blood biochemistry.

Eight patients became pregnant during the study, five of these in the 3 month follow-up period when contraception was mandatory. Three patients became pregnant in the late follow-up period more than 3 months after the last treatment. Seven patients delivered normal full term babies. One patient in the HAL 1% group who became pregnant in the extended follow-up period (>3 months after PDT) had an ectopic pregnancy and underwent therapeutic abortion.

Some deviations on the light source signal were reported, mainly from the patients upon removal of the device. These patients were allocated to all four treatment groups and included in the ITT analyses. The device deviation may have resulted in a reduced light dose delivery, but the deviations were not of any safety concern.

Conclusions

Cevira HAL PDT demonstrated a robust dose-response in patients with CIN2 supporting a further clinical investigation in phase 3 with HAL 5% as the dose of choice. The high and sustained HPV clearance across the populations suggests that further investigations in patients with cervical low-grade disease would be of interest.

No safety concerns were raised.

Date of the report: 26 September 2013