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: Not applicable		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal suppository		

Title of study: A randomized Phase II study of hexaminolevulinate (HAL) photodynamic therapy (PDT) in patients with low-grade cervical intraepithelial neoplasia (CIN1)

[redacted]

Study centres: This study was conducted in 6 centres: 4 centres in Germany, 1 centre in France and 1 centre in Norway

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

Studied period (years): Date main study started: 22 January 2009 Date main study completed: 27 October 2010	**Phase of development:** IIa

Objectives:

Primary Objectives

- To compare patient complete response rate of HAL PDT and placebo 6 months after last PDT in patients with low-grade cervical intraepithelial neoplasia (CIN).

Secondary Objectives

- To evaluate patient safety of HAL PDT in patients with low-grade CIN
- To compare complete response rate of HAL PDT and placebo 3 months after first PDT
- To compare the eradication rate of human papilloma virus (HPV) genotype after HAL PDT and placebo 6 months after last PDT

Methodology: This was a Phase IIa, prospective, randomized, placebo-controlled, double-blind, multicentre study of HAL or placebo PDT in patients with CIN1. The main study was carried out in 70 patients with CIN1 used laser-based photoactivation, while the study arm introduced in Amendment 5, involved 13 patients with CIN1/2 used a HAL ointment and an LED-based photo activation system. This study report includes only the results of the main study. The results in the population introduced in Amendment 5 will be reported separately due to the different nature of the treatment procedure used.

Patients who gave written informed consent were screened for the study. The first 70 eligible patients with local pathology of CIN1 were randomized in a ratio of 4:1:1 to administration of HAL vaginal suppository PDT, placebo vaginal suppository PDT and follow up only. Within 4 weeks of screening, patients in the groups randomised to HAL or placebo PDT, received HAL or placebo vaginal suppositories for 5 hours before illumination. Photoactivation was performed with red coherent light (633 nm) at doses of 50 J/cm^2 for 17 minutes. Patients randomised to follow-up underwent colposcopy but were not treated either with study drug or with red light illumination.

All patients were followed up with Pap smear and HPV testing at 3 and 6 months, as well as colposcopy and biopsy at 6 months after PDT.

Any patients in the HAL PDT or Placebo PDT treatment groups who had a non-complete response at Month 3 received a second PDT within 1 month using the same procedure as the first PDT. These patients were then followed up for response evaluation 3 and 6 months after the second PDT. Patients randomised to the Follow-up group underwent colposcopy but were not treated either with study drug or

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: Not applicable		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal suppository		

with red light illumination.

Number of patients (planned and analyzed):

Randomized treatment	*Planned*	*Actual (Intent-to-Treat and Safety Set*	*Actual (Per Protocol Population)*
		Number of Patients	
HAL suppository PDT	46	47	38
Placebo suppository PDT	12	12	11
Follow up only	12	11	10
Total	70	70	59

Diagnosis and main criteria for inclusion: Eligible patients were aged 18 years or older, with satisfactory colposcopy examination including visibility of the entire transformation zone including the squamocolumnar junction and visibility of entire lesion margin. Patients had ectocervical CIN1 as verified by local histology (biopsy), negative endocervical canal by colposcopy, and colposcopical visible lesion at Visit 2, before photoactivation. All patients gave written informed consent.

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

Hexaminolevulinate hydrochloride (HAL) 100 mg vaginal suppositories were applied for 5 hours followed by illumination with red light (633 nm) for 17 minutes giving a light dose of 50 J/cm^2.

Batch numbers: K9004 and K9017

Duration of treatment: Single dose. A second dose of randomized treatment could be given 3 to 4 months after the first dose for patients who had a partial response or stable disease at Month 3.

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

Placebo vaginal suppositories were applied for 5 hours followed by illumination with red light (633 nm) for 17 minutes giving a light dose of 50 J/cm^2.

Batch number: M8005

Criteria for evaluation:

Efficacy:

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

The primary endpoint was the percent of patients with complete response 6 months after the last PDT.

The secondary efficacy endpoints were the percent of patients in each group with complete response 3 months after the first PDT, and the percent of patients in each group with eradication of baseline HPV infection at 6 months after the last PDT.

The primary response endpoint analysis was based on local histology.

A responder was defined as a patient with normal histology and cytology. ASC-US cytology with negative HPV DNA was regarded as normal.

Safety: Safety variables were adverse events (AEs), haematology and biochemistry, and vital signs. The safety endpoints were the incidence of patients with AEs within 3 months of the last PDT, compared between treatment groups both for AEs, adverse drug reactions, and serious adverse events (SAEs).

Statistical methods:

The analysis of the primary endpoint was based on the exact Pearson chi-square test. The null-hypothesis was that HAL PDT and the Control group (Placebo PDT and Follow-up groups combined),

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: Not applicable		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal suppository		

had equal proportions of complete responders. The alternative hypothesis was that the proportions of complete responders in the two groups were different. Only if the null-hypothesis was rejected, the groups were tested pairwise for a difference in the proportion of complete responders. Secondary endpoints were analyzed using the same methods as the primary endpoint.

The safety parameters were presented descriptively and were summarized by treatment groups. As *ad hoc analyses*, Chi square test or Fisher's exact test was used where appropriate, to compare the incidence of AEs, adverse drug reactions and SAEs between the treatment groups.

SUMMARY – CONCLUSIONS

Demographics

The mean age of patients overall was 30.4 years (range 21 to 55 years), mean weight was 65.0 kg and mean height was 168.9 cm. Most patients were Caucasian (68 patients, 97.1%). Sixty patients (85.7%) completed the study as planned.

Efficacy Results

Primary Endpoint

The percentages of patients in the intent-to-treat (ITT) population, who were responders after 6 months was 42.6% in the HAL PDT group and 30.4% in the Control group (Placebo and Follow-up group combined). The difference between the groups was not statistically significant (p=0.435).

In the per protocol (PPS) population, the percentage of patients, who were responders after 6 months was 57.1% in the HAL PDT group and 25.0% in Control group. The difference between the HAL PDT group and the Control group was statistically significant (p=0.040).

Secondary Endpoints

The percentage of patients in the ITT population, who responded after 3 months was 48.9% in the HAL PDT group and 43.5% in the Control group. The difference was not statistically significant (p=0.80). The proportions of responders after 3 months were 52.6% in the HAL PDT group and 47.6% in the Control group (p=0.79).

In the ITT population, a total of 30 patients had high risk HPV DNA at screening. Of these, high risk HPV subtypes were eradicated 6 months after the first PDT in 60.0% of patients (n=20) in the HAL PDT group and 50.0% of patients (n=10) in the Control group. The differences between the HAL PDT group and Control group was not statistically significant (p=0.71). The results in the PPS population supported the findings in the ITT population: the proportions of patients with HPV eradication after 6 months were 73.3% in the HAL PDT group and 50.0% in the Control group (p=0.40).

Safety Results

The incidence of patients with at least one AE was 21 patients (44.7%) in the HAL PDT group, three patients (25.0%) in the Placebo PDT group and two patients (18.2%) in the Follow-up group. The most common AEs were muscle spasms (6.4% of patients in the HAL PDT group only), headache and uterine pain (both reported by 4.3% of patients in the HAL PDT group, and 8.3% of patients in the Placebo PDT group).

Treatment-related AEs were reported by 14 patients (30.0%) in the HAL PDT group, one patient (8.3%) in the Placebo PDT group and no patients in the Follow-up group. The most common treatment-related AEs reported by patients in the HAL PDT group were muscle spasms (6.4%), followed by uterine pain,

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: Not applicable		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal suppository		

dysmenorrhoea, and pain (4.3% each). The treatment-related AE in the Placebo PDT group was uterine pain.

Most AEs were mild or moderate. Four AEs in three patients were graded as severe. In the HAL PDT group, the severe AEs were jaw fracture, schizophrenia, and concomitant disease aggravated. In the Follow-up group, a severe AE of depression was reported. All of the severe AEs were also serious, but none were treatment-related. No other SAEs were reported. One patient was discontinued from the study due to pregnancy. Two patients in the HAL PDT group had illumination paused due to pain and cramps but both of these patients completed treatment.

Of the 38 AEs reported by the 21 patients in the HAL PDT group, two AEs occurred during insertion of the vaginal suppository and before illumination (cramping in both cases); 12 AEs occurred during or immediately after photoactivation (pain [6 cases], cramping [3 cases], and one case each of feeling of pressure, bleeding, and burning). Of the four AEs reported by patients in the Placebo group, one case of pain occurred during or immediately after photoactivation. All other AEs in both groups occurred more than 1 hour after photoactivation. Two AEs were reported by the Follow-up group (hypertension, depression).

No treatment-related AEs were ongoing at the end of the study.

There were no findings of note in laboratory safety variables or vital signs.

Conclusions

- Patients with CIN1 (PPS group) responded significantly better (57%) to HAL PDT compared with the Control group (25%) in this study.
- HAL PDT was generally well tolerated.

Date of the report: 22 October 2012

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor:
Photocure ASA</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Cevira</td></tr>
<tr><td>Name of Active Ingredient:
Hexaminolevulinate (HAL) vaginal ointment</td></tr>
<tr><td colspan="3">Title of study: A randomized Phase II study of hexaminolevulinate (HAL) photodynamic therapy (PDT) in patients with low/moderate grade cervical intraepithelial neoplasia</td></tr>
<tr><td colspan="3">[redacted]</td></tr>
<tr><td colspan="3">Study centres: This study was conducted in 3 centres: 2 centres in Norway and 1 centre in France</td></tr>
<tr><td colspan="3">Publications (reference): None at the time of writing this report.</td></tr>
<tr><td colspan="2">Studied period (years):
Start Part 2: 06 October 2010
Complete Part 2: 10 January 2012</td><td>Phase of development: IIa</td></tr>
<tr><td colspan="3">Study design: The study PC CE201/08 consists of two parts. In Part 1, 70 patients with CIN1 were treated with HAL PDT or placebo/follow-up only. HAL PDT was administered via vaginal suppositories and laser. The protocol was amended to include additional patients using the same study design, but with HAL administered as ointment and using a LED-based photo activation light source. The amended protocol also allowed patients with CIN2 to participate in Part 2 of the study. The results of Part 1 have been reported separately. The methodology and results of Part 2 are reported in the present report.</td></tr>
<tr><td colspan="3">Objectives: The objectives that apply to Part 2 of the study are:
To compare patient complete response rate of HAL PDT and placebo 6 months after last PDT in patients with CIN1 or 2.
To compare patient complete response rate of HAL PDT and placebo 3 months after first PDT.
To compare the eradication rate of human papilloma virus (HPV) genotype after HAL PDT and placebo 6 months after last PDT.
To evaluate patient safety of HAL PDT in patients with CIN1 or 2.</td></tr>
<tr><td colspan="3">Methodology: This was a Phase IIa, prospective, randomized, placebo-controlled, double-blind, multicentre study.

Patients who gave written informed consent were screened for the study. It was planned that 70 eligible patients with local pathology of CIN1 or CIN2 would be randomized in a ratio of 2:1 to receive HAL PDT or placebo respectively. However, due to difficulties in recruitment, this part of the study was stopped with 13 patients treated.

Within 4 weeks of screening, patients were randomized to receive vaginal HAL or placebo ointment administered by a new drug delivery system (Cevira device), 5 hours before illumination. The Cevira device was also the source of light for patients in the active treatment group. In the Placebo group the Cevira device was programmed not to provide light.

All patients were followed up with cytology and HPV testing at 3 and 6 months, as well as colposcopy and biopsy at 6 months after treatment.

Any patients in the HAL PDT or Placebo treatment groups who had a non-complete response at Month 3 received a second treatment within 1 month using the same procedure as the first. These patients were then followed up for response evaluation 3 and 6 months after the second treatment.</td></tr>
</table>

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: Cevira		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal ointment		

Number of patients (planned and analysed):

Randomized treatment	*Planned*	*Actual (All Patients Treated Population)*	*Actual (Per Protocol Population)*
		Number of Patients	
HAL PDT	46	10	5
Placebo	24	3	2
Total	70	13	7

Diagnosis and main criteria for inclusion: Eligible patients were aged 18 years or older, with satisfactory colposcopy examination including visibility of the entire transformation zone including the squamocolumnar junction and visibility of entire lesion margin. Patients had CIN1 or CIN2 as verified by local histology (biopsy), negative endocervical canal by colposcopy, and colposcopical visible lesion at Visit 2, before treatment initiation. All patients gave written informed consent.

Test product, dose and mode of administration, batch numbers: HAL HCl 5% ointment. A 2 g application (100 mg) was administered via the Cevira device followed 5 hours later by illumination with red light (630 nm) at a minimum dose of 50 J/cm^2 (mean ~100 J/cm^2) for 4.6 hours.

Batch numbers: HAL ointment K0003, Cevira device PC001.

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

Reference therapy, dose and mode of administration, batch numbers: A 2 g application of placebo ointment was administered via the Cevira device, but was not followed by red light illumination. The Cevira device was programmed to not provide any light in the Placebo group.

Batch numbers: Placebo ointment K0002, Cevira device PC001.

Criteria for evaluation:

Efficacy:

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

The primary endpoint was the percentage of patients with complete response 6 months after the last PDT.

The other efficacy endpoints were the percentage of patients in each group with complete response 3 months after the first PDT, and the percentage of patients in each group with eradication of baseline HPV infection at 6 months after the last PDT.

The primary response endpoint analysis was based on local histology.

A complete responder was defined as a patient with normal histology and cytology. ASC-US cytology with negative HPV DNA was regarded as normal.

Safety:

Safety variable was adverse events (AEs). The safety endpoints were the incidence of patients with AEs within 3 months of the last PDT, compared between treatment groups both for AEs, adverse drug reactions, and serious adverse events (SAEs).

Statistical methods: Due to the low number of included patients no statistical analysis was performed. Efficacy and safety parameters were presented descriptively and were summarised by treatment group.

Demographics: The mean age of patients overall was 37.0 years (range 25 to 60 years), mean weight was 67.3 kg and mean height was 167 cm. All of the patients were Caucasian. Eleven patients had CIN1

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: Cevira		
Name of Active Ingredient: Hexaminolevulinate (HAL) vaginal ointment		

at baseline, while two had CIN2. All except one patient completed the study including a 6 month follow up. Two patients, one from each group, had a second PDT. One patient in the Placebo group was discontinued at the 3-month follow-up visit because of disease progression (CIN3). No patients were withdrawn due to AEs.

Efficacy results

At 6 months after last treatment, nine of the 10 patients in the HAL PDT group presented with a normal biopsy and/or cytology and eradication of high-risk HPV, as compared to one of three in the Placebo group.

Three months after the first treatment six of 10 patients in the HAL PDT group and two of three in the Placebo group were responders.

Two out of four patients in the HAL PDT group and one out of three patients in the Placebo group showed HPV eradication at 6 months after the last treatment.

Safety results

AEs were reported by seven patients (70%) in the HAL PDT group, and two patients (67%) in the Placebo group. The most common AEs were back pain and headache, which were each reported by two patients: both cases of back pain were reported in patients in the HAL PDT group, headache was reported by one patient in each group.

Treatment-related AEs were reported by three patients, all of whom were in the HAL PDT group: discomfort, vaginal discharge, and pelvic pain. The onset of pelvic pain was during insertion of the Cevira device, the onset of discomfort and of vaginal discharge was more than 1 hour after administration. All of the other AEs occurred post-treatment.

All of the AEs were mild or moderate. There were no severe AEs, SAEs, treatment discontinuations or treatment interruptions due to AEs.

One patient in the HAL PDT group became pregnant during the study. The outcome of the pregnancy was missed (or spontaneous) abortion. The abortion was not considered related to the study treatment.

Conclusions

The treatment was well tolerated and showed promising efficacy in patients with CIN1/2, but efficacy and safety have to be verified in a larger study.

Date of the report: 25 July 2012