# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-415**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology/Biopharmaceutics Review

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| **NDA:** | 21-415 |
| **SUBMISSION TYPE:** | Original NDA |
| **SUBMISSION DATE:** | September 27, 2001 |
| **PRODUCT:** | Metvix® 168mg/g (methyl aminolevulinate) Cream |
| **INDICATION:** | Actinic Keratosis |
| **SPONSOR:** | PhotoCure ASA, Norway |
| **US AGENT:** | Clementi Associates, PA |
| **REVIEWER:** | Tapash K. Ghosh, Ph.D. |

## 1. EXECUTIVE SUMMARY

Metvix® cream contains methyl aminolevulinate hydrochloride. Addition of methyl aminolevulinate to human skin leads to temporary accumulation of photoactive porphyrins (PAP) via the heme biosynthetic pathway. When photoactive porphyrins are exposed to light of an appropriate wavelength in the presence of oxygen, a photochemical reaction takes place. This results in production of singlet oxygen, which destroys intracellular components, in particular the mitochondria, leading to cell death. The activation of photosensitizers with resultant cytotoxicity forms the basis of photodynamic therapy (PDT) of pre-malignant or malignant cells.

Photoactive porphyrins formed after topical application of methyl aminolevulinate are believed to be localized specifically in pre-malignant and malignant tumors of epithelial origin.Therefore, application of Metvix® cream to actinic (solar) keratoses causes selective photosensitization confined to the target lesions. Subsequent illumination of lesions with the CureLight lamp leads to destruction of target lesions without risk to surrounding normal skin.

Photodynamic therapy for actinic keratoses with Metvix cream is a two-stage process involving (1) superficial preparation of the lesions followed by application of Metvix® cream to target lesions for 3 hours under occlusive dressing, and (2) removal of the dressing and rinsing off excess cream followed by illumination with red light of wavelength 570 to 670 nm for about 8 minutes and total light dose of 75 J/cm$^2$ using the CureLight lamp.

No pharmacokinetic studies have been conducted *per se* due to the instability of methyl aminolevulinate hydrochloride in serum. Two studies evaluated the skin and lesion pharmacokinetics of methyl-aminolevulinate hydrochloride and PAP: **101/97** and **206/98.** These studies were used for the initial assessment of Metvix Cream concentration and application time. In absence of direct measurement of the extent of

systemic exposure to methyl aminolevulinate hydrochloride after topical application of Metvix cream, PAP fluorescence was used as surrogate to assess the PK of methyl aminolevulinate hydrochloride following application of Metvix cream in these clinical studies. However, the fluorescence methodology used was not rugged and validated properly.

The degree of systemic absorption and skin uptake are not adequately characterized to support the dosage and administration of Metvix Cream (168 mg/g) proposed by the sponsor. Based on the surrogate efficacy data measured by unvalidated analytical technique and limited clinical response data submitted in Section 6 (Clinical Pharmacology and Biopharmaceutics) of this NDA, dosing regimen proposed in the label can not be substantiated from Clinical Pharmacology and Biopharmaceutics point of view on the optimal dosing method (time and amount). Therefore, additional dose-ranging data using validated analytical methodology are requested.

**1.1 Recommendation**

At this time the applicant has not adequately assessed the in vivo bioavailability of methyl-levulinic acid or levulinic acid (the active form of methyl-levulinic acid). A new in vivo bioavailability study, using both a validated analytical method and proper site preparation procedures (consistent with those used in the clinical trials) should be conducted using the clinical dose of Metvix Cream.

Based on the submitted data, it is not possible to determine whether the dose and conditions are optimized. That is, the reasoning for selection of the 168-mg/gm dose and the application time (period from application of the cream to photo-activation) is unclear. It is possible that a lower dose under optimized conditions may provide equal or more benefit than the 168-mg/gm dose. Should additional clinical trials be initiated in support of this application, then the applicant should be encouraged to re-evaluate the safety and efficacy of lower doses.

Tapash K. Ghosh, Ph.D.
Pharmacokineticist, DPE III

Team Leader: E. Dennis Bashaw, Pharm.D. _____

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HFD-880(Bashaw/Ghosh)
HFD-880 (Lazor/Selen)

To DFS

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## 3. SUMMARY OF CPB FINDINGS

Dermal penetration of radiolabeled methyl aminolevulinate applied to human skin has been studied *in vitro (Study 1555/13).* The mean cumulative penetration through human skin was 0.26% of the administered dose after 24 hours and the radioactivity forming a depot in the skin was 4.9% of the applied dose. Penetration was linear after a lag time of 1.6 hours. The extent of systemic absorption has not been determined in humans directly. However, based on *in vitro* data, it has been calculated that less than 0.02% of the applied dose will penetrate human skin and enter the systemic circulation after a 3-hour application of Metvix® cream (*Reviewed by Pharmacology/Toxicology Reviewer*).

According to the sponsor, it became evident from *in vitro* penetration studies in rat and human skin and from whole body autoradiography studies in rats that only a very small amount of methyl aminolevulinate hydrochloride could be expected to penetrate the skin in patients. Accordingly, the expected amounts of aminolevulinate (ALA) and PAP in serum formed from methyl aminolevulinate hydrochloride would be much lower than what could be determined by the available analytical methods. Although the failure of the assay for methyl aminolevulinate prevented generation of pharmacokinetic data, it is extremely unlikely that such information would have any relevance to the safety of topically applied Metvix cream. The reasons relate to both the low systemic exposure to methyl aminolevulinate and the known high therapeutic index of 5-ALA and PAP.

In absence of direct measurement of the extent of systemic exposure to methyl aminolevulinate hydrochloride after topical application of Metvix cream, PAP fluorescence was used as surrogate to assess the PK of methyl aminolevulinate hydrochloride following application of Metvix cream in two clinical studies listed below. These studies were used for the initial assessment of Metvix Cream concentration and application time. The studies are:

- **PC T101/97:** An open exploratory (Phase I/II) study of P-1202 160 mg/g cream in patients with nodular basal cell carcinoma.

- **PC T206/98:** A pharmacokinetic study of protoporphyrin IX formation in patients with actinic keratosis and basal cell carcinoma after topical application of P-1202 cream

Data generated from studies 101/97 and 206/98 were used to select the range of cream concentrations and duration of application in a clinical Phase I/II study in AK patients **(PC T202/98).** The data from all 3 studies were subsequently used to select a standard dosing regimen for the treatment of AK. Studies 101/97 and 206/98 are reviewed in detail whereas a very brief review has been made for study 202/98.

Studies 206/98 and 202/98 used 168 mg/g methyl aminolevulinate, while study 101/97 used 160 mg/g methyl aminolevulinate. This minor difference is not considered to have any impact on the human pharmacokinetics and bioavailability data presented. Thus, all information obtained with the 160 mg/g formulation is relevant to the 168 mg/g formulation.

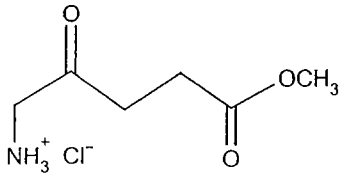
Given both the topical nature of the product, the pattern of use, and the limited surface area involved, drug interaction studies with Metvix cream were not performed.

## 4. QUESTION-BASED REVIEW

### 4.1 General Attributes

***What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?***

Metvix® cream is an oil in water emulsion (pH = — containing methyl aminolevulinate 168 mg/g. Methyl aminolevulinate hydrochloride is a white to slightly yellow powder that is freely soluble in water and methanol, soluble in ethanol and practically insoluble in most organic solvents. The chemical formula for methyl aminolevulinate HCl is $C_6H_{11}NO_3 \cdot HCl$ (MW=181.62) and it has the following structural formula:



Clinical studies were conducted using three different concentrations of Metvix cream at concentrations of 16 mg/g, 80 mg/g and 168 mg/g, as well as placebo cream. The 168 mg/g is identical to the formulation proposed for marketing as shown below:

| Name of Ingredient | Placebo | 16 mg/g | 80 mg/g | 168 mg/g |
|---|---|---|---|---|
| **Active** | | | | |
| Methyl aminolevulinate Hydrochloride Equivalent to: Methyl aminolevulinate | 0 | 16 | 80 | 168 |
| **Excipients** | | | | |
| Glyceryl Monostearate BP | | | | |
| Cetostearyl Alcohol NF | | | | |
| Polyoxyl Steartae NF | | | | |
| Methylparaben NF | | | | |
| Edetate Disodium USP | | | | |
| Glycerin USP | | | | |
| White Petrolatum USP | | | | |
| Cholesterol NF | | | | |
| Isopropyl Myristate NF | | | | |
| Peanut Oil NF | | | | |
| Almond Oil | | | | |
| Oleyl Alcohol NF | | | | |
| **Total** | 1000 | 1000 | 1000 | 1000 |

***What are the proposed therapeutic indication, dosage, route of administration and mechanism of drug action?***

*Indication*: Metvix cream in combination with red light illumination using the CureLight lamp is indicated for the topical treatment of non-hyperkeratotic actinic keratoses.

Actinic keratoses (AK) are premalignant skin lesions that occur mainly in sun-exposed areas such as the face, scalp, or dorsum of the hands. The lesions are skin-colored or reddish-brown macules or papules, usually 3 to 10 mm in diameter, with dry, rough, adherent scale. Their histology is typified by dysplasia of keratinocytes in the lower third of the epidermis and frequently by increased pigment in the epidermis. Despite the view that not all AK lesions need to be treated, a consensus guideline recommends treatment to avoid development of skin malignancy, particularly squamous cell carcinoma (SCC).

*Mechanism of Action of Metvix-PDT*

Methyl aminolevulinate is an ester of 5-aminolevulinic acid (5-ALA), an endogenous early precursor in the biosynthesis of heme. 5-ALA is formed in the mitochondria from glycine and succinyl CoA by the enzyme 5-aminolevulinic synthase. Two molecules of 5-ALA are then condensed to form the first intermediate, porphobilinogen. In mammals the heme synthesis pathway occurs in the mitochondria and in the cytosol and takes place in all nucleated cells.

The heme synthesis pathway is regulated by an inhibitory action of heme on the synthesis of 5-ALA. Therefore, the flux regulation of the heme synthesis pathway can be overruled by supplying exogenous 5-ALA or derivatives thereof, e.g., methyl aminolevulinate. Since the formation of heme from PpIX is also regulated, addition of 5-ALA or derivatives thereof will lead to the accumulation of photoactive intermediates including protoporphyrin IX (PpIX), henceforth referred to as PAP. PAP are photoactive, fluorescing compounds. Upon light activation of PAP in the presence of oxygen, singlet oxygen is formed, which causes damage to cellular components, in particular the mitochondria.

The intracellular accumulation of PAP such as PpIX is measured directly by virtue of their natural property of fluorescence. Most esters of 5-ALA result in a greater accumulation of intracellular fluorescence than 5-ALA. The rate of 5-ALA/5-ALA ester-induced porphyrin synthesis has been shown to be higher in malignant and premalignant cells and tissues than in their normal counterparts. Furthermore, fluorescence has been shown to be more selectively localized in tumor cells after application of methyl aminolevulinate than after 5-ALA treatment. This greater selectivity is a desirable property with regard to both efficacy and safety since normal skin and other tissues are unaffected.

These observed differences are not fully understood and can only be explained partly; they may be due to differences in tissue penetration and distribution, in cellular uptake mechanism, and activation of the heme synthesis enzymes. Using the partition coefficient as a measure for lipophilicity it has been shown that methyl aminolevulinate penetrates

skin twice as efficiently as 5-ALA. There is limited knowledge about the cellular uptake mechanism for methyl aminolevulinate. However, methyl aminolevulinate seems to have a different uptake mechanism than 5-ALA, and this might be one explanation for the difference in selectivity.

The extent of possible cleavage of the methyl ester to 5-ALA in plasma has not been investigated directly, but the inability to provide a validated assay in serum was attributed to the instability of methyl aminolevulinate hydrochloride in this medium. This suggests that systemic exposure if present is likely to be transient. The concentration of endogenous 5-ALA in human plasma has been reported to be 10 to 60 ng/mL. If the instability of methyl aminolevulinate was due to 100% conversion to 5-ALA after or during penetration, it can be calculated that the rise of 5-ALA concentration in patient plasma would be insignificant.

In summary, methyl aminolevulinate is selectively absorbed by the lesion and is subsequently converted to PAP in the mitochondria of proliferating epithelial cells. PAP are activated by light of the appropriate wavelength. For Metvix-PDT, red light in the range 570 to 670 nm is used, which is within the visual spectrum. Upon activation of light in the presence of oxygen, singlet oxygen is formed which causes damage to intracellular compartments, in particular the mitochondria, leading to cell death possibly by apoptosis.

### 4.2 General Clinical Pharmacology

***Are the active moieties in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?***

No. During the development of this product, an attempt was made to develop an assay for methyl aminolevulinate in serum. However, according to the sponsor, difficulties were encountered with the bioanalytical method for methyl aminolevulinate in both rat and human serum using — In human serum samples, methyl aminolevulinate was shown to be unstable in serum at room temperature and during freeze/thaw. Recoveries were less than —. Intra- and interassay coefficients of variation were over — Therefore, it proved impossible to obtain serum profiles of methyl aminolevulinate in human serum.

***How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients? Are the study populations relevant to the proposed indication?***

The mode of therapy could not be tested on healthy volunteers. They were studied on patients with Actinic Keratosis (AK) and basal cell carcinoma (BCC). Although this NDA is for the AK indication, the sponsor claimed that data from studies conducted in BCC are relevant because both AK and BCC are lesions generally confined to the epidermis situated above an intact basement membrane. Therefore the function of an

intact basement membrane is preserved in both types of lesions. The study of PAP accumulation in BCC lesions is also important because the formation of PAP in relation to the margins of the lesions was examined.

***Are dosage and dosing regimen appropriate for the treatment of the proposed indication?***

Based on the surrogate efficacy data measured by unvalidated analytical technique and limited clinical response data submitted in Section 6 (Clinical Pharmacology and Biopharmaceutics) of this NDA, dosing regimen proposed in the label can not be substantiated from Clinical Pharmacology and Biopharmaceutics point of view.

**4.3 Intrinsic Factors**

The efficacy and safety of PDT with Metvix cream 168 mg/g have not been established in pediatric patients. Solar AK is extremely uncommon in pediatric population mainly below 18 years of age. The sponsor states in the cover letter that PDT with Metvix cream 168 mg/g does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients. The sponsor requested a full waiver of the requirement for pediatric use information. Patients in the AK studies had an age range between 71 and 89. The study was conducted with 7 males and 1 female.

**4.4 Extrinsic Factors**

The intensity and wavelength of light as well as illumination time are crucial factors in this therapy. Proper calibration of the light source as well as proper training of the technician are highly recommended. CDRH has reviewed the device component separately.

**4.5 General Biopharmaceutics**

***Is to-be-marked formulation equivalent to clinical formulation?***

Clinical studies were conducted using three different concentrations of Metvix cream at concentrations of 16 mg/g, 80 mg/g and 168 mg/g, as well as placebo cream. The 168 mg/g is identical to the formulation proposed for marketing.

**4.6 Analytical**

***What bioanalytical methods are used to assess the amount of methyl aminolevulinate in blood, urine, skin, residual cream or other study specimens?***

According to the sponsor, difficulties were encountered with the bioanalytical method for methyl aminolevulinate in both rat and human serum using — — in human serum samples, methyl aminolevulinate was shown to be unstable in serum at room temperature and during freeze/thaw. Recoveries were less than — Intra- and interassay coefficients of variation were over — . Therefore, it proved impossible to obtain serum profiles of methyl aminolevulinate in human serum.

In study **PC T206/98**, *surface skin fluorescence* was used as surrogate for PK/efficacy. A — fluorescence spectrometer equipped with a red-sensitive photomultiplier tube was used. Tissue surface fluorescence was measured using an excitation light wavelength of 407 nm and emission of 637 nm. The sponsor was asked to provide validation report on this measurement technique. In their communication dated December 12, 2001, they mentioned a pilot study with three healthy volunteers who received 5-ALA or methyl aminolevulinate and a summary table containing data from these three patients were included. The reviewer asked for individual data from these three pilot patients and also instrument calibration data. In the sponsor's final communication on May 3, 2002, data from four (previously mentioned three) healthy subjects were included to address different parameters of skin fluoresecence including specificity, drift over time, assay precision etc. Significant inter-individual variation was observed which according to the sponsor could be overcome by using values relative to the value measured at time 0 for each individual. Moreover, while assay precision for large surface was good, it was poor for small and curved surfaces.

In study **PC T101/97**, *fluorescence in biopsies* was used as surrogate for PK/efficacy and the sponsor stated that *no validation* for this technique was done except that they followed a literature reported technique.

***Are analytical methods sensitive enough to determine the extent of systemic absorption of methyl aminolevulinate after topical application?***

No.

## 5. DETAILED LABELING RECOMMENDATIONS

The following changes are recommended. ~~ABC~~ suggests deletion of text and *ABC (italics)* suggests insertion of new text.

__/9__ Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

__✓__ § 552(b)(5) Draft Labeling

# 6.2 Individual Study Reviews

**NDA: 21-415/Study PC T101/97** **Study Date: June, '97 - Oct, '98**

***An Open Exploratory (Phase I/II) Study of P-1202 160 mg/g Cream in Patients with Nodular Basal Cell Carcinoma***

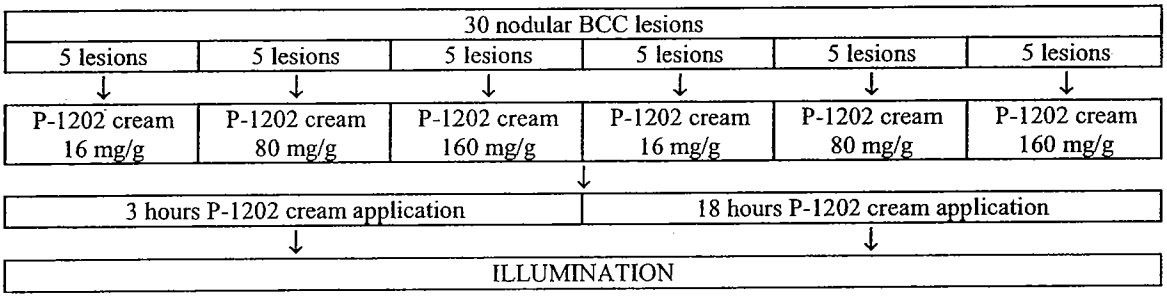
## Objectives

Primary : To determine the optimal P-1202 cream dosage regimen for treating nodular BCC lesions based on the formation of PpIX in the lesion. The effect of the treatment will be determined as PpIX fluorescence after 3 or 18 hours of cream application.

Secondary : To determine safety and tolerability of P-1202, 16 mg/g, 80 mg/g and 160 mg/g and to determine the objective response rate to P-1202 based PDT in patients with nodular BCC.

## Study Design

This study was an open, phase I/II single center study, where six different dosage regimens were tested in nodular BCC lesions as per the flowchart below. Maximum three lesions were treated with different cream concentrations for each patient.




The P-1202 cream, either 16 mg/g, 80 mg/g or 160 mg/g, was applied on the lesion (as an approximately 1 mm thick layer surrounding 1 cm outside the lesion) and covered with an occlusive Tegaderm dressing for either 3 hours or 18 hours. If a patient had 3 lesions to be treated, one lesion was treated with 16 mg/g, one with 80 mg/g, and one with 160 mg/g P-1202. After 3 hours or 18 hours, respectively, the cream was removed, and a biopsy of the lesion was taken in order to determine the penetration depth of the P-1202. The biopsy was immediately immersed in liquid nitrogen and stored in a freezer -80°C. Finally, the lesion was exposed to a light dose of 75 J/cm$^2$.

Efficacy was assessed as PpIX fluorescence in the biopsies of the BCC induced by topical application of 16 mg/g, 80 mg/g or 160 mg/g P-1202 for 3 hours or for 18 hours. The fluorescence was presented for segments of 0.2 mm from the surface to the bottom of the lesions. Microscopic fluorescence photometry was performed using an [redacted] microscope with a 100 W mercury lamp. The fluorescence images were recorded by a highly light-sensitive [redacted] camera (resolution: 385 x 578 pixels with a dynamic range of 16 bits per pixel). The fluorescence of P-1202 induced PpIX in the segments of lesions was quantified by an image processing unit. The penetration of P-1202-induced porphyrins in the lesions was measured by the PpIX fluorescence in the biopsies. Fluorescence distribution measurement in the biopsies was the primary parameter.

Macroscopic evaluation of response rate on BCC was performed 6-8 weeks after light treatment. The response rate was evaluated as complete (100%), partial (≥ 50%) or no healing (< 50%). Safety was assessed by adverse events and by haematological and biochemical parameters.

**Disposition of patients and lesions**

Eight patients, 5 males and 3 females, were treated with P-1202 cream for 3 hours, mean age 67.2 years, and 8 patients, 6 males and 2 females, were treated with P-1202 cream for 18 hours, mean age 71.5 years. Altogether, 16 patients with 44 lesions were included. The pathologist verified by histological analysis 32 lesions to be nodular BCC. Determination of fluorescence penetration is based on the 32 lesions verified as nodular BCC. Determination of objective response is presented for the 32 nodular BCC lesions, plus for 11 lesions (12 minus 1, this one lesion was not evaluated due to incorrect treatment procedure) with superficial BCC.

## Results

*Efficacy:*

The background fluorescence in untreated tissue varied from 600 to 750 ( 668 ± 36). In the efficacy evaluation, a fluorescence higher than 740 (mean + 2 SD) is considered as fluorescence induced by study medication and all calculations are based on fluorescence values larger than 740.

The primary objective of this study was to determine the optimal cream strength and exposure time that results in a maximal penetration of P-1202 measured as PpIX fluorescence in the lesions, without inducing PpIX formation in normal surrounding tissues. The effects of cream strength and exposure time on depth of fluorescence in the lesions are shown in Table 1. After 3 hours treatment the mean depths of fluorescence for the P-1202 cream 16, 80 and 160 mg/g treatment groups were 0.7, 1.0 and 1.3 mm respectively. The corresponding values for the 18 hours treatment groups were 0.5, 1.0 and 0.8 mm. However, it should be noted that the lesions treated for 3 hours were significantly (p=0.02) deeper than the lesions treated for 18 hours, Table 2. Mean lesion depths for the 3 hours treatment groups of P-1202 cream 16 mg/g, 80 mg/g and 160 mg/g

were 1.5 mm, 1.6 mm and 1.4 mm. The corresponding values for the 18 hours treatment groups were 1.0 mm, 1.1 mm and 1.3 mm. Due to the observed differences in lesion depths between the 3 and 18 hours treatment groups, the fluorescence distribution was not directly compared. The relative depth of fluorescence, i.e. [depth of fluorescence] / [depth of lesion] x 100%, rather than the absolute fluorescence values was compared for the different treatment groups. Relative depths of fluorescence are presented in Table 3. It can be seen that for P-1202 cream 16 mg/g there was no difference between 3 and 18 hours application time (relative depth of fluorescence 56±37% and 52± 44%, respectively). With regards to P-1202 cream 80 mg/g, the relative depth of fluorescence was better after 18 hours application (88±22%) than after 3 hours application (62±39%). In the case of the P-1202 cream 160 mg/g, the relative depth of fluorescence was found to be better after 3 hours application (98±4%) than after 18 hours application time (67±37%). In addition, P-1202 cream 160 mg/g applied for 3 hours was the only treatment group where the relative depth of fluorescence was more than 90% in all lesions treated, Table 3.

**Table 1: Depth of fluorescence (mm) of lesions with a fluorescence ≥ 740, by cream strength and application time.**

| Cream Concentration | 3 hours | | | | | 18 hours | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd |
| 16 mg/g | 5 | 0.70 | | | 0.41 | 5 | 0.50 | | | 0.42 |
| 80 mg/g | 5 | 1.00 | | | 0.58 | 5 | 0.96 | | | 0.25 |
| 160 mg/g | 6 | 1.34 | | | 0.49 | 6 | 0.83 | | | 0.59 |

**Table 2: Depth of lesion (mm), by cream strength and application time.**

| Cream Concentration | 3 hours | | | | | 18 hours | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd |
| 16 mg/g | 5 | 1.54 | | | 0.59 | 5 | 1.00 | | | 0.19 |
| 80 mg/g | 5 | 1.56 | | | 0.46 | 5 | 1.00 | | | 0.16 |
| 160 mg/g | 6 | 1.38 | | | 0.53 | 6 | 1.25 | | | 0.40 |

**Table 3: Relative depth of fluorescence (%) (depth of fluorescence/ depth of lesion) of lesions with a fluorescence ≥ 740, by cream strength and application time.**

| Cream Concentration | 3 hours | | | | | 18 hours | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd |
| 16 mg/g | 5 | 55.71 | | | 36.56 | 5 | 51.97 | | | 43.96 |
| 80 mg/g | 5 | 61.50 | | | 39.20 | 5 | 88.18 | | | 21.70 |
| 160 mg/g | 6 | 98.33 | | | 4.08 | 6 | 66.89 | | | 36.60 |

Fluorescence intensity in different depth levels of the lesions are shown in Tables 4 and 5. For P-1202 cream 16 mg/g the mean fluorescence distribution through the lesions seem identical after 3 and 18 hours treatment. The mean fluorescence intensities through the lesions after treatment with P-1202 cream 80 mg/g were somewhat higher for 18 hours compared to 3 hours. The mean fluorescence distribution through the lesions after application of P-1202 cream 160 mg/g did not show any major differences between 3 and 18 hours application time.

**Table 4: Fluorescence intensity for different depth levels of lesions with a fluorescence ≥ 740 , by cream strength. Application time 3 hours.**

| Lesion Depth | 16 mg/g | | | | | 80 mg/g | | | | | 160 mg/g | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd |
| 0-200 | 4 | 885.75 | | | 261.60 | 4 | 884.00 | | | 284.30 | 6 | 968.50 | | | 216.72 |
| 201-400 | 4 | 1057.50 | | | 153.57 | 4 | 1093.75 | | | 187.86 | 6 | 1084.67 | | | 245.97 |
| 401-600 | 4 | 1199.75 | | | 215.30 | 4 | 1095.25 | | | 128.17 | 6 | 1064.00 | | | 235.07 |
| 601-800 | 4 | 916.75 | | | 26.89 | 4 | 942.00 | | | 117.04 | 6 | 1001.50 | | | 228.89 |
| 801-1000 | 2 | 751.50 | | | 2.12 | 4 | 929.25 | | | 137.55 | 6 | 1121.80 | | | 223.78 |
| 1001-1200 | 0 | 0 | | | 0 | 3 | 970.33 | | | 145.96 | 6 | 1113.20 | | | 107.68 |
| 1201-1400 | 0 | 0 | | | 0 | 2 | 814.50 | | | 72.83 | 2 | 1002.50 | | | 27.58 |
| 1401-1600 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 2 | 855.50 | | | 40.31 |
| 1601-1800 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 2 | 854.00 | | | 42.43 |
| 1801-2000 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 1 | 786.00 | | | 0 |

**Table 5: Fluorescence intensity for different depth levels of lesions with a fluorescence ≥ 740, by cream strength. Application time 18 hours.**

| Lesion Depth | 16 mg/g | | | | | 80 mg/g | | | | | 160 mg/g | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd | n | Mean | Min | Max | Sd |
| 0-200 | 5 | 885.60 | | | 142.16 | 5 | 1195.80 | | | 256.10 | 6 | 911.00 | | | 194.14 |
| 201-400 | 2 | 1229.50 | | | 45.96 | 5 | 1434.60 | | | 435.72 | 6 | 1181.17 | | | 279.99 |
| 401-600 | 2 | 1143.50 | | | 30.41 | 5 | 1427.60 | | | 511.71 | 3 | 128.00 | | | 154.88 |
| 601-800 | 2 | 928.50 | | | 136.47 | 4 | 1374.75 | | | 463.17 | 3 | 1380.00 | | | 369.14 |
| 801-1000 | 1 | 903.00 | | | 0 | 4 | 1121.00 | | | 358.40 | 3 | 1072.33 | | | 176.53 |
| 1001-1200 | 1 | 770.00 | | | 0 | 1 | 1640.00 | | | 0 | 1 | 1060.00 | | | 0 |
| 1201-1400 | 0 | 0 | | | 0 | 1 | 1562.00 | | | 0 | 1 | 917.00 | | | 0 |
| 1401-1600 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 1 | 779.00 | | | 0 |
| 1601-1800 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 1 | 780.00 | | | 0 |
| 1801-2000 | 0 | 0 | | | 0 | 0 | 0 | | | 0 | 1 | 848.00 | | | 0 |

Fluorescence values in normal tissue (Table 6) are generally higher for the 18 hours treatment groups than the 3 hours treatment groups, for all three cream strengths. The higher fluorescence in normal tissue indicates a lack of selective PpIX formation in the lesions when the cream is applied for 18 hours.

**Table 6: Fluorescence in normal tissue, by cream strength and application time, according to evaluation by the pathologist.**

| Cream Concentration | 3 hours | | | | | 18 hours | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Fluorescence in normal tissue | | | | | Fluorescence in normal tissue | | | | |
| | n | No | Little | Some | Much | n | No | Little | Some | Much |
| 16 mg/g | 5 | 3 | 1 | 1 | 0 | 5 | 0 | 0 | 1 | 4 |
| 80 mg/g | 5 | 2 | 2 | 1 | 0 | 5 | 2 | 0 | 1 | 2 |
| 160 mg/g | 6 | 1 | 3 | 1 | 1 | 6 | 0 | 0 | 0 | 6 |

*Clinical Response*:

The clinical response of the PDT at 6-8 weeks after treatment, is presented in Table 7. For most of the lesions the investigators scored the response as partial both after 3 hours treatment and 18 hours treatment. Four lesions were scored as complete, two treated with

160 mg/g P-1202 cream for 3 hours before illumination, one treated with 80 mg/g and one with 160 mg/g P-1202 cream for 18 hours before illumination.

**Table 7: Evaluation of lesions verified by the pathologist to be nodular BCCs, by cream strength and application time.**

| Cream Concentration | 3 hours | | | | 18 hours | | | |
|---|---|---|---|---|---|---|---|---|
| | Response on BCC | | | Total | Response on BCC | | | Total |
| | Complete (100%) | Partial (>50%) | None (<50%) | N | Complete (100%) | Partial (>50%) | None (<50%) | N |
| 16 mg/g | 0 | 4 | 1 | 5 | 0 | 4 | 1 | 5 |
| 80 mg/g | 0 | 4 | 1 | 5 | 1 | 4 | 0 | 5 |
| 160 mg/g | 2 | 4 | 0 | 6 | 1 | 5 | 0 | 6 |

## Discussion and Conclusions

Based on the efficacy data obtained in this study, taking into account lesion depth, depth of PpIX fluorescence and relative depth of PpIX fluorescence Table 3, 4 and 5, it appears that P-1202 cream 160 mg/g applied for 3 hours gave the best penetration, whereas P-1202 cream 80 mg/g applied for 18 hours was second best. Mean relative depth of fluorescence for the two regimens were 98±4% and 88±22% respectively. In addition, higher fluorescence in normal surrounding tissue was found for all cream strengths after 18 hours treatment compared to 3 hours treatment. Based on limited clinical response data and subjective nature of evaluation, it is difficult to distinguish between 80 mg/g and 160 mg/g regimen. For most of the lesions the investigators scored the response as partial both after 3 hours treatment and 18 hours treatment with all three concentrations tested.

According to the sponsor, only two patients reported adverse events during cream application, mild burning skin and mild pain. Therefore, the safety profile for P-1202 cream, independent of P-1202 cream concentration and application time, is considered good.

## Comments:

- *The sponsor claims that on the basis of the efficacy and safety discussed above, 3 hours treatment with P-1202 cream 160 mg/g was the best treatment regimen tested. The sponsor's conclusion is based on relative depth of fluorescence measurements. However, without taking the depth of lesion into consideration and evaluating the original fluorescence data (Table 4 and 5), it appears that the mean fluorescence distribution in the lesions after application of P-1202 cream 80 mg/g (884) and 160 mg/g (969) did not show any major differences after 3 hours application time. Also it has been observed that the mean fluorescence distribution through the lesions after application of P-1202 cream 160 mg/g did not show any major differences between 3 (969) and 18 hours (911) application time. Therefore, while the sponsor claims that 3 hours treatment with P-1202 cream 160 mg/g was the best treatment regimen tested, based on the available data 3 hours treatment with P-1202 cream 80 mg/g will work as well. The reviewer believes that there is no significant difference between 80 mg/g*

*and 160 mg/g for 3 hours regimen. Moreover, in the light of observed higher fluorescence in normal tissue when the cream is applied for 18 hours (i.e., lack of selectivity at 18 hours) , and in absence of any major difference in the clinical response profiles of 80 mg/g and 160 mg/g regimens (too few data and subjective scoring) recommendation of 80 mg/g for 3 hours seems more justifiable and conservative.*

- *The clinical response rate with all three concentrations are poor as for most of the lesions the investigators scored the response as partial both after 3 hours treatment and 18 hours treatment.*

- *Measurement techniques are unvalidated and vague. The term depth is used in different contexts with different implications. For example, depth of lesion (mm) in Table 2, depth of fluorescence (mm) in Table ,1 whereas lesion depth (with no unit) in Tables 4 and 5.*

- *The information on how long the lesions were illuminated are not available.*

- *No systemic adverse events were evaluated.*

- *Considering unvalidated technique and very limited number of patients involvement (i.e., the study may not be appropriately powered), no conclusion can be drawn from this study in terms of stated objectives.*

**NDA: 21-415/Study PC T206/98** **Study Date: Sep, '98 – Apr, '99**

***A Pharmacokinetic Study of Proto-porphyrin IX Formation in Patients with Actinic Keratosis and Basal Cell Carcinoma After Topical Application of P-1202 Cream***

## Objectives

Primary: To compare the fluorescence of protoporphyrin IX (PpIX) at different time intervals in superficial BCC and in AK after topical application of P-1202 cream, placebo (only AK), 16 mg/g, 80 mg/g and 160 mg/g.

Secondary: To determine safety, response rate and other pharmacokinetic parameters in patients with superficial BCC and in patients with AK after topical application of P-1202 placebo cream, P-1202 cream 16 mg/g, 80 mg/g and 160 mg/g.

## Study Design

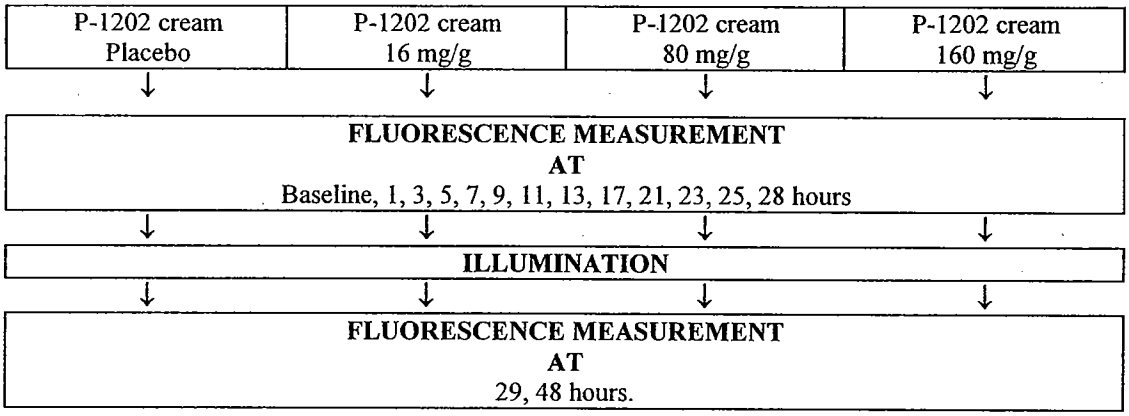
This study was a prospective, randomized, double-blind, single center study. Photodynamic therapy (PDT) was performed within 14 days after the pre-treatment evaluation visit. Prior to administration of the P-1202 cream, the lesion was prepared in order to facilitate access of P-1202 cream and light to all parts of the lesion. In superficial lesions, crusts were removed by a small curette and the surface of the lesion was scraped gently in order to roughen the surface. The P-1202 cream, 16 mg/g, 80 mg/g, 160 mg/g or placebo cream, was applied on the lesion as an approximately 1 mm thick layer and about 10 mm of the surrounding normal tissue, and the area was covered by an adhesive, occlusive dressing (Tegaderm). In addition, the lesions were covered with a black material to protect the lesions from any light during the test period. The fluorescence measurements were performed through the dressing. The lesion number and the center of the lesion were marked at the dressing, in order to place the probe for fluorescence measurements. The patients were treated only once. The cream was applied to the lesions for 28 hours in order to measure the PpIX fluorescence at selected time intervals. After 28 hours, the occlusive dressing was removed and the excessive cream was gently cleaned off with saline solution. Illumination was performed immediately after removal of the dressing and the cream from the skin. The skin area that was covered with cream was illuminated with red light with a fluency of 75 J/cm$^2$. The lamp emitted red light using a 150 W halogen lamp, which is collimated by means of an elliptical mirror and focused by a lens through various filters, which removes infrared light, i.e. heat, and produced the appropriate wavelength band (570-680 nm) to a circular area, 30-55 mm in diameter with the following time and intensity (Table 1).

**Table 1: PDT information. Illumination time and light intensity.**

| Lesion group | cream conc.(mg/g) | Illumination time (min) | | | | | Light intensity (mW/cm2) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mean | std | min | max | n | mean | std | min | max | n |
| AK group | 0 | 8.4 | 1.4 | | | 8 | 165.9 | 25.9 | | | 8 |
| | 16 | 8.4 | 2.1 | | | 8 | 159.9 | 28.6 | | | 8 |
| | 80 | 8.4 | 1.4 | | | 8 | 149.0 | 33.0 | | | 8 |
| | 160 | 8.3 | 2.8 | | | 8 | 162.6 | 35.3 | | | 8 |
| BCC group | 16 | 8.1 | 0.7 | | | 7 | 157.7 | 15.7 | | | 7 |
| | 80 | 6.6 | 2.6 | | | 7 | 173.9 | 15.0 | | | 7 |
| | 160 | 8.9 | 2.3 | | | 7 | 155.1 | 41.2 | | | 7 |

The lay out of the study design is described in Table 2 below. Each BCC patient was treated with P-1202 cream, 16mg/g (Batch : 0195P/P3, 0301P/P1), 80 mg/g (Batch : 0196P/P4) and 160 mg/g (Batch : 0197P/P7) on three different lesions, respectively. Each AK patient was treated with P-1202 cream, 16mg/g, 80 mg/g, 160 mg/g and placebo (Batch : 0194P/P), on four different lesions, respectively.

*Table 2: Cream application and fluorescence measurements*




Totally, 15 patients were included in the study. In each of the seven 8 AK patients, 4 AK lesions were treated and in each of the 7 BCC patients 3 BCC lesions were treated. However only six patients were included in the BCC fluorescence analysis as one patient was excluded due to blood in the lesions. The Demographic and Disposition of subjects are summarized in the following Table 3.

**Table 3: Demographic and Disposition of Subjects**

| Lesion Group | N | Age (years) | Sex | Included in he Fluorescence analysis | Included in the Clin. Resp. analysis | Included in the Safety analysis |
|---|---|---|---|---|---|---|

| Lesion Group | | N | Mean | SD | Min | Max | N | % | N | % | N | % | N | % | N | % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AK | 8 | 8 | 79.1 | 6.3 | 71 | 89 | 1 | 25 | 7 | 75 | 8 | 100 | 8 | 100 | 8 | 100 |
| BCC | 7 | 7 | 73.4 | 8.1 | 58 | 84 | 4 | 57 | 3 | 43 | 6 | 86 | 7 | 100 | 7 | 100 |
| Total | 15 | 15 | 76.4 | 7.5 | 58 | 89 | 5 | 33 | 10 | 67 | 14 | 93 | 15 | 100 | 15 | 100 |

*Safety, Efficacy and Pharmacokinetic Assesments*

*Efficacy* was assessed as PpIX fluorescence (excitation light of 407 nm and the resulting fluorescence at 637 nm using a Perkin Elmer LS-5 fluorescence spectrometer equipped with a red-sensitive photomultiplier tube (Hamamatsu R 928) at two sites of untreated normal skin, two sites of treated normal skin and two lesion sites, at baseline and at 1, 3, 5, 7, 9, 11, 13, 17, 21, 23, 25, 28 hours after topical application of P-1202 cream placebo (only for AK lesions), 16 mg/g, 80 mg/g or 160 mg/g. In addition, PpIX fluorescence was measured one hour after illumination (at 29 hours), and at 48 hours if the patient was willing to return to the hospital the day after. A clinical evaluation of the lesion was done 6 weeks after the PDT. The response to treatment was determined as complete clearance of the lesions, or not.

*Safety* was assessed in terms of adverse events (AEs). Local phototoxicity was reported as an AE. Local skin reactions/phototoxicity were assessed during and after P-1202 cream application and illumination.

*Pharmacokinetic* evaluation was scheduled to be performed from the measurement of serum P-1202, ALA and PpIX to document possible systemic absorption of P-1202 by measurements of P-1202 metabolites, ALA and PpIX, after topical application of P-1202. However a validation study of the analytical method for P-1202 showed that the method could not be used due to instability of P-1202 in rat and human serum.

## Results:

**Pharmacokinetic Analysis of Data:** According to the sponsor, an independent pharmacokinetic (PK) analysis (*Population PK analysis*) of the data from this study has been performed. The specific objectives of this analysis were to establish a PK model able to describe and predict the fluorescence-time profiles obtained in this study. Secondary objectives were to use this model to estimate PpIX formation constant(s); magnitude of maximum level and time to reach maximum level. Furthermore, it was an objective to use the model to uncover expected (cream concentration and exposure time) and other possible co-variates as P-1202 cream concentration and lesion type.

According to the sponsor, the population-PK analysis performed indicated that the pharmacokinetics of PpIX fluorescence after P-1202 cream application in skin lesions can be described by a model with pseudo zero order absorption of P-1202 (mimicking a constant infusion) coupled with a saturable transformation of P-1202 to PpIX fluorescence and 1st. order elimination of PpIX fluorescence. Unfortunately, in spite of specific request made by the reviewer to submit more

information on the development and validation of the model, the sponsor did not povide any further information. The sponsor commented that because of high diversity in the PpIX fluorescence from the lesions, it was difficult to make accurate predictions using the PK population model.

***Analysis of Efficacy***

AK lesions:Mean and median PpIX fluorescence in treated lesions and in normal treated skin surrounding the lesions after application of P-1202 cream, are presented in Table 4 and 5 respectively. From 1 to 21 hours the mean PpIX fluorescence measurements increased 142%, 211% and 197% for P-1202 cream 16 mg/g, 80 mg/g and 160 mg/g respectively. Even in normal treated skin surrounding the AK lesions, there was 74% and 143% increase in PpIX fluorescence with 80 mg/g and 160 mg/g respectively after 21 hours of P-1202 cream application. The increase of PpIX fluorescence in all lesions was quite rapid initially and at approximately 10 hours a plateau was reached. No increase in PpIX fluorescence was observed for the placebo group.

**Table 4: Mean PpIX Fluorescence Measurements in AK Lesions by Time and Dose Groups**

| | Cream Concentration | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 mg/g | | 16 mg/g | | 80 mg/g | | 160 mg/g | |
| Parameters | Mean ± SD (CV%, min, max) | | Mean ± SD (CV%, min, max) | | Mean ± SD (CV%, min, max) | | Mean ± SD (CV%, min, max) | |
| T (h) | AK | Ted | AK | Ted | AK | Ted | AK | Ted |
| 1 | 30.3±5.7 (23, | 31.0±5.2 (17, | 37.9±9.9 (26. | 34.8±5.8 (17. | 37.5±15.8 (42, | 29.0±3.9 (13 | 38.1±12.3 (32, 24.5, 59.6) | 27.3±3.1 (11 |
| 3 | 26.7±5.1 (19. | 28.6±4.3 (15, | 59.9±47 (78, | 34.1±5.6 (16 | **56.8±36.6 (64, 24.1, 119.7)** | 31.5±5.1 (16 | **61.4±28.4 (46, 27.6, 102.7)** | 30.2±5.5 (18 |
| 5 | 26.3±5.4 (21, 18.5, 34.0) | 27.8±4.7 (17, | 78.1±77 (99, | 35.3±5.3 (15 | 68.1±55.5 (81 | 32.8±8.0 (24. | 78.2±42.8 (55, 27.6, 144.0) | 35.6±12.4 (35, |
| 21 | 24.2±3.5 (14, | 28.0±5.0 (18, | 92±59 (64 | 34.1±6.3 (15, | **116.8±95.1 (81,** | 50.5±12.0 (24. | **113.1±60.5 (53, 36.9, 231.9)** | 66.3±43.3 (65. |

**Table 5: Median PpIX Fluorescence Measurements in AK Lesions by Time and Dose Groups**

| T (h) | Placebo | | | 16 mg/g | | | 80 mg/g | | | 160 mg/g | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | AK | Ted | Uted | AK | Ted | Uted | AK | Ted | Uted | AK | Ted | Uted |
| 0 | 30.2 | 32.4 | 22.1 | 36.2 | 37.4 | 21.5 | 30.6 | 33.2 | 22.7 | 27.6 | 28.9 | 22.2 |
| 1 | 30.7 | 29.8 | 22.9 | 36.8 | 35.4 | 20.3 | 37.9 | 28.6 | 21.2 | 35.3 | 28.0 | 20.7 |
| 3 | 26.0 | 28.1 | 19.7 | 38.5 | 34.1 | 19.5 | **46.6** | 33.5 | 21.4 | **54.5** | 29.6 | 21.0 |
| 5 | 27.4 | 28.1 | 21.9 | 44.0 | 35.7 | 20.4 | 42.5 | 34.1 | 21.6 | 73.7 | 35.4 | 22.3 |
| 7 | 24.3 | 25.4 | 20.1 | 46.5 | 36.1 | 20.2 | 72.5 | 37.6 | 21.1 | 91.3 | 37.0 | 21.1 |
| 9 | 25.7 | 30.5 | 20.6 | 49.4 | 36.1 | 19.7 | 75.4 | 36.6 | 21.5 | 102.0 | 35.7 | 21.2 |
| 11 | 25.1 | 27.0 | 21.5 | 55.1 | 38.5 | 19.1 | 64.5 | 37.8 | 21.9 | 91.9 | 38.2 | 21.3 |
| 13 | 24.6 | 28.7 | 20.6 | 59.0 | 31.5 | 19.6 | 70.2 | 37.3 | 21.3 | 115.6 | 44.4 | 22.4 |
| 17 | 26.5 | 26.9 | 22.6 | 68.8 | 31.8 | 19.4 | 85.5 | 37.3 | 21.5 | 65.6 | 62.5 | 20.9 |
| 21 | 24.0 | 28.3 | 21.3 | 88.8 | 32.4 | 19.9 | **86.3** | 56.2 | 22.0 | **103.3** | 50.6 | 22.1 |
| 23 | 22.2 | 25.4 | 20.6 | 109.5 | 31.0 | 19.2 | 82.4 | 57 | 21.8 | 108.3 | 54.5 | 23.0 |
| 25 | 22.6 | 23.9 | 21.5 | 108.7 | 29.7 | 19.8 | 83.5 | 57.0 | 22.0 | 100.1 | 56.1 | 22.4 |
| 28 | 21.6 | 21.5 | 20.6 | 89.2 | 31.5 | 19.4 | 108.0 | 60.3 | 22.7 | 89.6 | 47.9 | 23.0 |
| 29 | 13.4 | 14.9 | 17.0 | 20.1 | 16.9 | 17.1 | 30.9 | 25.1 | 18.9 | 29.1 | 33.2 | 18.3 |
| 48 | 13.7 | 19.7 | - | 22.7. | 24.0 | - | 19.8 | 19.5 | - | 35.4 | 18.7 | - |

**AK – Actinic Keratosis lesions; Ted – Treated Skin; Uted – Untreated normal skin**

BCC lesions: Mean and median PpIX fluorescence in treated lesions and in normal treated skin surrounding the lesions after application of P-1202 cream, are presented in Table 6 and 7 respectively. From 1 to 21 hours the mean PpIX

fluorescence measurements increased 137%, 246% and 255% for P-1202 cream 16 mg/g, 80 mg/g and 160 mg/g respectively. In normal treated skin surrounding the BCC lesions, there was 63%, 60% and 70% increase in PpIX fluorescence with 16 mg/g, 80 mg/g and 160 mg/g respectively after 21 hours of P-1202 cream application. No increase in PpIX fluorescence was observed for the placebo group.

**Table 6: Mean PpIX Fluorescence Measurements in BCC Lesions by Time and Dose Groups**

| | Cream Concentration | | | | | |
|---|---|---|---|---|---|---|
| | 16 mg/g | | 80 mg/g | | 160 mg/g | |
| Parameters | Mean ± SD (CV%, min, max) | | Mean ± SD (CV%, min, max) | | Mean ± SD (CV%, min, max) | |
| T (h) | BCC | Ted | BCC | Ted | BCC | Ted |
| 1 | 41.6±16.9 (41, —) | 34.3±6.6 (19 — ) | 44.6±21.8 (49, —) | 34.4±9.5 — | 31.9±7.7 — | 28.4±5.2 — |
| 3 | 58.1±39.4 (68, —) | 37.5±10.1 (27 — ) | 72.7±60.1 (83 —) | 34.3±5.7 — | 45.9±22.1 — | 29.3±7.4 — |
| 5 | 69.6±40.5 (58, —) | 40.4±13.5 (33 — ) | 98.5±87.6 (89, —) | 35.3±5.7 — | 59.5±31.0 — | 33.2±11.9 — |
| 21 | 98.6±47.0 (48, —) | 55.9±45.3 (81 — ) | **154.3±111.8** — | 55.0±32.2 — | **113.7±50.0** — | 48.2±26.2 — |

**Table 7: Median PpIX Fluorescence Measurements in BCC Lesions by Time and Dose Groups**

| T (h) | 16 mg/g | | | 80 mg/g | | | 160 mg/g | | |
|---|---|---|---|---|---|---|---|---|---|
| | BCC | Ted | Uted | BCC | Ted | Uted | BCC | Ted | Uted |
| 0 | 32.0 | 38.3 | 21.0 | 30.9 | 37.2 | 21.5 | 30.2 | 31.1 | 22.6 |
| 1 | 38.1 | 37.8 | 16.7 | 38.0 | 36.1 | 20.4 | 30.2 | 28.6 | 21.3 |
| 3 | 44.1 | 36.2 | 20.0 | **49.7** | 35.2 | 19.8 | **37.8** | 30.4 | 17.3 |
| 5 | 57.8 | 37.9 | 17.8 | 65.3 | 35.8 | 19.6 | 56.9 | 30.4 | 19.6 |
| 7 | 55.7 | 36.6 | 19.8 | 74.5 | 35.3 | 22.8 | 76.7 | 30.6 | 21.8 |
| 9 | 63.5 | 35.5 | 19.6 | 89.0 | 34.7 | 20.6 | 90.5 | 33.8 | 20.5 |
| 11 | 75.7 | 40.2 | 18.3 | 91.3 | 39.7 | 21.0 | 121.7 | 33.3 | 21.4 |
| 13 | 86.9 | 32.7 | 18.8 | 99.4 | 38.7 | 20.4 | 108.0 | 33.0 | 20.0 |
| 17 | 116.5 | 30.3 | 16.8 | 111.4 | 38.0 | 14.9 | 109.1 | 24.8 | 17.7 |
| 21 | 96.3 | 37.4 | 19.9 | **130.4** | 48.8 | 20.7 | **109.8** | 44.4 | 21.7 |
| 23 | 104.3 | 38.9 | 20.6 | 131.6 | 49.7 | 21.9 | 121.1 | 42.8 | 22.6 |
| 25 | 90.2 | 44.8 | 20.2 | 11.9 | 47.4 | 20.7 | 130.2 | 46.6 | 22.9 |
| 28 | 78.0 | 34.2 | 20.1 | 1193 | 46.4 | 20.6 | 132.4 | 38.5 | 20.7 |
| 29 | 27.3 | 20.9 | - | 20.7 | 16.8 | - | 21.4 | 17.2 | - |

**BCC – Basal ell Carcinoma lesions; Ted – Treated Skin; Uted – Untreated normal skin**

***Selectivity:***

Comparing the mean PpIX fluorescence intensity in all lesions (AK and BCC) and surrounding treated normal skin showed that PpIX fluorescence was more pronounced (1.5 – 3 fold) in lesions than in normal skin ( Tables 4, 5, 6 and 7) indicating selective absorption of PpIX in the lesions. However, no remarkable difference was observed between treated and untreated skin areas.

***Photobleaching:*** Photobleaching was shown in all lesions. After illumination with a light dose of 75 J/cm$^2$ at the end of the application period, PpIX fluorescence in the lesions returned to baseline levels (Table 8).

**Table 8: PpIX Fluorescence Values Registered Before Cream Application and After Illumination.**

| Lesion group | Cream conc. (mg/g) | N | Fluorescence in lesions | |
|---|---|---|---|---|
| | | | Before cream application | After illumination |

| | | 8 | Median | Min | Max | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|
| AK group | 0 | 8 | 30.2 | | | 13.4 | | |
| | 16 | 8 | 36.2 | | | 20.1 | | |
| | 80 | 8 | 30.6 | | | 30.9 | | |
| | 160 | 8 | 27.6 | | | 29.1 | | |
| BCC group | 16 | 7 | 32.0 | | | 27.3 | | |
| | 80 | 7 | 30.9 | | | 20.7 | | |
| | 160 | 7 | 30.2 | | | 21.4 | | |

***Clinical Response:*** All lesions were illuminated about 28 hours after P-1202 cream application according to illumination time and light intensity presented in Table 1. Most lesions were illuminated for about 8 minutes with mean light intensity 149-174 mW/cm$^2$. The light dose was 75 J/cm$^2$. The objective clinical response of the PDT 6 weeks after treatment, is presented in Table 8. It appears that P-1202 cream 80 mg/g resulted in maximum complete response compared to P-1202 cream 16 mg/g and 160 mg/g in both AK and BCC lesions.

**Table 9: Clinical Response**

| Lesion group | Cream conc. (mg/g) | N | Lesion response | | | |
|---|---|---|---|---|---|---|
| | | | CR Complete response | | non-CR Non complete response | |
| | | 8 | n | % | n | % |
| AK group | 0 | 8 | 1 | 13 | 7 | 88 |
| | 16 | 8 | 2 | 25 | 6 | 75 |
| | 80 | 8 | 7 | 88 | 1 | 13 |
| | 160 | 8 | 4 | 50 | 4 | 50 |
| BCC group | 16 | 7 | 4 | 57 | 3 | 43 |
| | 80 | 7 | 5 | 71 | 2 | 29 |
| | 160 | 7 | 4 | 57 | 3 | 43 |
| Total | 0 | 8 | 1 | 13 | 7 | 88 |
| | 16 | 15 | 6 | 40 | 9 | 60 |
| | 80 | 15 | 12 | 80 | 3 | 20 |
| | 160 | 15 | 8 | 53 | 7 | 47 |

**Discussion :** The data on PpIX fluorescence show selective induction of PpIX fluorescence in AK and BCC lesions, both compared to placebo and normal treated skin after topical application of P-1202 cream 16 mg/g, 80 mg/g and 160 mg/g. The data from PpIX fluorescence measurement and clinical response rate in both AK and BCC, dosing regimen of P-1202 cream 80 mg/g and 160 mg/g were indistinguishable. The parameters at 3 and 21 hours are bolded in Tables 4 –7 for quick comparison. Moreover clinical response data, though scanty (Table 9) shows a better response rate for 80 mg/g over 160 mg/g in both AK and BCC lesions.

Complete photobleaching using a light dose of 75 J/cm$^2$ for about 8 minutes was observed after 28 hours application of all three P-1202 cream concentrations.

These results combined with the reporting of only expected, transient, mostly mild, and local phototoxicity events during and after illumination indicate that 75 J/cm$^2$ is an effective and safe light dose to be used in PDT with P-1202 cream.

**Conclusion**

It is concluded that application of P-1202 creams with all three concentrations (16 mg/g, 80 mg/g and 160 mg/g) induces lesion specific PpIX formation in AK and BCC lesions. Both AK and BCC lesions treated with P-1202 cream 80 mg/g showed the highest rate of complete response, 80%. For 160 mg/g complete response was reported for 53%, while for 16 mg/g the figure was 40%. In addition, a light dose of 75 J/cm$^2$ of red light (570-670 nm) applied for about 8 minutes is considered sufficient for full photoactivation of PpIX after application of all three P-1202 cream concentrations. Lastly, the results show that PDT with P-1202 cream is well tolerated with only expected local phototoxicity related to the treatment.

**Comments:**

- *80 mg/g appears to be the best both from PpIX fluorescence data and clinical response data.*
- *It is not clear why no systemic AE was measured*
- *As the sponsor commented that because of high diversity in the PpIX fluorescence from the lesions, it was difficult to make accurate predictions using the PK population model, the report on that aspect was not reviewed. The review was also not possible anyway as the sponsor failed to submit the documents (**AP1**: Summary of report from Population modeling and **AP4**: Printout of population modeling files) required for such review in their original submission and a subsequent fax request on March 18, 2002.*
- *It appears that methodology used to measure fluorescence in study 206 is different from that used in study 101. For example, in 101, fluorescence was measured from biopsy samples whereas in 206, fluorescence was measured directly from treated lesions. Overall, the measurement technologies are complex and were not adequately validated.*
- *Sufficient dose-ranging has not been documented.*

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**NDA: 21-415/Study PC T202/98** **Study Date: Aug, '98 – Nov, '99**

## *An Open Exploratory (Phase I/II) Study of MetvixCream 80 mg/g and 160 mg/g in Patients with Primary Actinic Keratosis*

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In this dose-range finding Phase I/II study, the primary objective was to determine the mean patient response rate (percentage of lesions in complete response within a patient) in patients with primary AK at 3 months after having received 1 or 2 treatments with Metvix Cream using 4 different treatment regimens. Secondary objectives were to determine the mean patient response rate after one treatment using the different regimens; lesion response rate, cosmetic outcome, and recurrence rate after 12 months of lesions that showed a complete response; and safety.

This was an open-label, randomized, parallel-group study conducted at 8 European sites. A total of 112 patients were randomized to 1 of 4 treatment groups: Metvix 80 mg/g Cream applied for 1 hours or 3 hours or Metvix 168 mg/g Cream applied for 1 hour or 3 hours prior to illumination with non-coherent light (570 to 670 nm) and 75 J/cm$^2$. In patients with inadequate responses after 2 months, treatment was repeated, with assessment of response after a further 3-month follow up.

Efficacy data were evaluable in 110 patients (25 to 30 per group) with a total of 380 treated lesions. The groups were well-matched for demographic factors and location and size of lesions, of which 87% were on the face or scalp. Table 1 summarizes the results.

**Table 1: Patient and Lesion Response Rates in Study 202/98**

| Metvix Dose and Application Time | Patient Response Rates After 1 or 2 Treatments * Mean (95% CI) | Patient Response Rates After 1 Treatment* Mean (95% CI) | Overall Lesion Complete Response Rate After 1 or 2 Treatments | Overall Lesion Complete Response Rate After 1 Treatment | Lesion Complete Response Rates for Thin Lesions on Face/Scalp After 1 or 2 Treatments |
|---|---|---|---|---|---|
| 80 mg/g 1 hour | 69% (53-85) | 49% (32-67) | 74% | 54% | 86% |
| 168 mg/g 1 hour | 74% (60-88) | 54% (38-70) | 76% | 58% | 78% |
| 80 mg/g 3 hour | 73% (57-89) | 49% (31-66) | 77% | 55% | 88% |
| 168 mg/g 3 hour | 88% (78-97) | 71% (57-84) | 85% | 70% | 96% |

* Number of lesions with complete response divided by number of lesions.

A trend of little increased mean patient response rate with dose (concentration of cream and duration of application prior to photoactivation) was seen with the data. However, there were *no statistically significant differences* between treatment groups.

## Comments:

*In absence of statistically significant differences between treatment groups, the basis for proceeding with 3h 168 mg/g regimen for further clinical testing is not clear.*

# 6.3. OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics

*NEW DRUG APPLICATION FILING AND REVIEW FORM*

*General Information About the Submission*

| | Information | | Information |
|---|---|---|---|
| **NDA Number** | 21-415 | **Brand Name** | Metvix Cream |
| **OCPB Division (I, II, III)** | III | **Generic Name** | Methyl Aminolevilinate |
| **Medical Division** | 540 | **Drug Class** | Keratolytic |
| **OCPB Reviewer** | Tapash K. Ghosh | **Indication(s)** | Non Hyperkeratolytic Actinic Keratosis |
| **OCPB Team Leader** | Dennis Bashaw | **Dosage Form** | Topical 168 mg/g Cream |
| | | **Dosing Regimen** | Site specific |
| **Date of Submission** | 9/26/01 | **Route of Administration** | Topical |

| Estimated Due Date of OCPB Review | 3/26/02 | Sponsor | Photocure |
|---|---|---|---|
| PDUFA Due Date | 9/26/02 | Priority Classification | 1S |
| Division Due Date | | | |

## Clin. Pharm. And Biopharm. Information

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | | | |
| **Tabular Listing of All Human Studies** | X | | | |
| **HPK Summary** | X | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | **Needs to be submitted** |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| ***Healthy Volunteers-*** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | X | 3 | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD:** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD:** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability:** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies:** | | | | |
| **Dissolution:** | | | | |
| **(IVIVC):** | | | | |
| **Bio-wavier request based on BCS** | | | | |

| | | | | |
|---|---|---|---|---|
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 3 | | |
| | | | | |

| Filability and QBR comments | | |
|---|---|---|
| | "X" if yes | **Comments** |
| Application filable ? | X | Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? |
| Comments sent to firm ? | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. |
| QBR questions (key issues to be considered) | | |
| Other comments or information not included above | | |
| Primary reviewer Signature and Date | Tapash Ghosh 11-14-01 | |
| Secondary reviewer Signature and Date | | |

*CC: NDA XX-XXX, HFD-850(Electronic Entry or Lee), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR (B. Murphy)*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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Tapash Ghosh
7/19/02 12:54:51 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/19/02 02:52:34 PM
BIOPHARMACEUTICS