

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-415

MEDICAL REVIEW(S)

Review Addendum for NDA 21-415
Team Leader Summary

July 26, 2004

NDA 21-415 was originally submitted on September 26, 2001 for methyl aminolevulinate cream, 16.8%, for use with the PhotoCure CureLight Broadband Lamp, a medical device that was submitted for review as a PMA in CDRH (P010061). The indication of the drug/device combination was for the photodynamic treatment of non-hyperkeratotic actinic keratoses of the face and scalp.

The initial application was found to be approvable on September 19, 2002. There were multiple complete response issues in the initial action letter. These included requests for additional safety data with regard to contact sensitization, inadequate labeling to allow for safe and effective use of this product, and post-marketing studies for a longer-term clinical study (See September 19, 2002 action letter for specifics).

In response to the Approvable letter, an amendment was submitted on July 16, 2003, that was a complete response to the above issues. This amendment included additional data to support safe use of the product for the sought indication. The complete response amendment contained information to support a markedly improved and comprehensive label (see approvable action letter from CDER dated January 16, 2004). However, the information submitted in the July, 2003 response resulted in additional device concerns (these concerns included device calibration and the need for a stopping mechanism to prevent movement of the control panel during operation). Further, a commitment to conduct post-marketing studies as described in the January, 2004, Approvable letter remained outstanding.

On May 27, 2004, the Applicant submitted a complete response to the January, 2004, Approvable letter. With this most recent submission cycle (a 2 month cycle) a safety update and a commitment to conduct the needed post-marketing studies was included. Additionally, the Applicant agreed to the label as crafted and negotiated in the prior review cycle.

The INDICATIONS AND USAGE section of the label as discussed with the Applicant states the following:

“**TRADENAME** Cream in combination with 570 to 670 nm wavelength red light illumination using the CureLight Broadband Model CureLight 01 lamp is indicated for treatment of non-hyperkeratotic actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation (debridement using a sharp dermal curette) in the physician’s office when other therapies are unacceptable or considered medically less appropriate.”

CMC

The CMC reviewer noted in his January 9, 2004, review that a question of Tradename (methyl aminolevulinate) Cream sterility arose during the review of NDA 21-415 "when it became known that, in the course of preparation of the treatment site prior to application of the drug product, the skin surface was abraded to enhance absorption." This issue was resolved in a subsequent team meeting and in consultation with the microbiology reviewer, with a conclusion that this drug product was not required to be sterile.

The current labeling indicates that this product is for immunocompetent patients.

It is noted that the drug product has a relatively short expiration dating as proposed by the Applicant (18 months when packaged in — tubes and 15 months when packaged in — tubes). Factors which may have contributed to this include the

As a labeling issue, the Applicant was requested to provide information that would support the safe use of this product with gloves. Specific information was requested regarding which glove would allow for the safest use, given the wide extent of sensitization observed in dermal safety testing. It was concluded by the CMC reviewer that butyl nitrile gloves would likely provide adequate protection to healthcare workers who are required to administer the drug product. Latex and vinyl gloves were determined to be inadequate for this purpose.

Pharm/Tox

The Pharm/Tox reviewer, Dr. Paul Brown, succinctly states the non-clinical safety issues relevant to clinical use in his review (dated October 1, 2003):

"The animal toxicology data indicates that methyl ALA has the potential to induce hepatotoxicity at sufficient doses. The NDA did not originally contain sufficient data on the monitoring of liver enzymes in the human studies. Therefore, the — was included in the label. If the human data in the current submission is considered sufficient to address the potential for hepatotoxicity then the — may be removed from the label."

The current iteration of labeling has this data removed from the label as the human data was considered sufficient to address the potential for hepatotoxicity at internal team discussions.

Clinical Pharmacology/Biopharmaceutics

As stated by the Clinical Pharmacology reviewer, Dr. Tapash Ghosh:

"While the Sponsor did conduct a number of in vivo biopharmaceutics studies as part of their original NDA, the studies themselves did not, in the Agency's opinion, demonstrate in a definitive manner that the 168 mg dosing regimen was the optimal regimen." It was determined that part of the problem was the wide separation of dosing.

It was previously agreed that this informational need could be addressed in a post-marketing study (see below).

Such information as derived from what is essentially a preliminary post-marketing dose finding study may be useful for future drug development for the Applicant. Clinical efficacy data for any new concentration would need to be derived from further clinical study.

Clinical and Devices

As was carefully stated in the Clinical Review by Dr. Brenda Vaughan (January 14, 2004 review):

“An *Approval* recommendation is being made for NDA 21-415 for use of methyl aminolevulinate-PDT in treatment of non-hyperkeratotic actinic keratosis (AK) of the face and scalp when used as supplementary to curettage in non-immunocompromised patients in the physician’s office when other therapies are unacceptable or considered less appropriate. Approval as second line therapy is being recommended due to the high rate of sensitization of TRADENAME Cream and lack of retreatment and adequate long-term safety data. This application is for a drug-device combination and approval is contingent upon an approval recommendation from CDRH for the PhotoCure™ Halogen PDT Lamp Model CureLight 01.”

At the time of that review, CDRH approval had not been achieved due to certain device concerns. These concerns were addressed resulting in Mr. Felton’s review dated April 20, 2004. As Mr. Felton indicates:

“The device described in this PMA is a broad spectrum light source having an output wavelength of 570-650 nm. This wavelength is generated by passing the output of a halogen lamp through a series of IR filters, a focusing lens, and a cooling system. The device has an illumination spot size diameter of 35-55 mm and is capable of a dose rate of 200 mW/cm² generating a total fluence for treatment of 75 J/cm². As part of the light delivery system, the device comes with a horseshoe shaped aiming device to define the correct spot size and a calibration probe which is used to insure the correct dose rate for the selected spot size. Both of these devices come with removable, disposable plastic sleeves used to prevent cross contamination between patients.”

The current draft CDRH recommendation for this device is for Approval; however, the review and Approval letter have not yet been signed off as of the date of this Summary.

A post-marketing commitment is recommended on the part of Clinical to address longer-term safety and treatment of larger lesions of actinic keratoses. See below.

Post-marketing Commitments

PhotoCure has committed to conducting the following studies in the timeframes as below:

1. Conduct a systemic bioavailability study following application of methyl aminolevulinate cream with different concentrations ranging between 80 and 168 mg/g (preferably 80, 100, 120, 140 and 168 mg/g) in patients with multiple (8 – 10) actinic keratosis lesions. Please revise your previously submitted protocol to include the amount of TRADENAME Cream used (number of tubes and amount used from each tube) as well as the total body surface area in cm² treated for each patient.

Protocol Submission: August, 2004

Study Start: January, 2005

Final Report Submission: December, 2006

2. Conduct a 12-month safety study in at least 200 evaluable patients with 10 or more actinic keratosis lesions with diameters of ≥ 4 mm, documenting the effects of retreatment of lesions with partial response and treatment of new lesions. In this study, representative numbers of patients with higher Fitzpatrick skin types, e.g. Asians and Hispanics, should be included. Location of lesions should be sufficiently identified for long-term follow-up. The gram amount of TRADENAME Cream applied with each treatment session should be documented. Laboratory parameters should be collected, and patients should be monitored for photoallergic skin reactions.

Protocol Submission: August, 2004

Study Start: January, 2005

Final Report Submission: December, 2006

Conclusion

In conclusion, an Approval recommendation is being given for this application. The Agency had discussed and helped the Applicant address a variety of concerns since the original filing of this Application. All of these concerns were relevant to the use of this product in the United States. The Sponsor has agreed to the above post-marketing study commitments. Final approval is still pending CDRH approval of the device which remains outstanding at the time of this Summary.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

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

/s/

Markham Luke

7/27/04 12:15:32 PM

MEDICAL OFFICER

Clinical Team Leader Multi-Disciplinary Summary. See also Dr. Huene's
review of the Safety Update information. PM: Please
forward a copy of signed off Summary to
Mr. Richard Felton, CDRH

Jonathan Wilkin

7/27/04 12:21:00 PM

MEDICAL OFFICER

I concur with approval recommendation.

Document ID: N-000(BZ)

Correspondence date: May 25, 2004
CDER Stamp date: May 27, 2004

MEDICAL OFFICER'S REVIEW OF AMENDMENT TO NDA 21-415

DATE: June 21, 2004

SPONSOR: PhotoCure ASA
Oslo, Norway

DRUG: Methyl aminolevulinate hydrochloride cream + photodynamic
therapy (PDT)

INDICATION: Actinic keratoses

DATE OF AMENDMENT: May 25, 2004

TYPE OF AMENDMENT: Complete response (Type I resubmission)

The sponsor has provided in this amendment a Complete Response to all outstanding issues, as were specified in the Approvable letter of January 16, 2004. The response includes the following items.

- 1) Final draft labeling.
- 2) A Safety Update.
- 3) A commitment to perform two Phase 4 studies, as outlined.

In addition, the sponsor has provided a synopsis of the procedures and results of a sensitization study, designated Study PC T112/03.

The draft labeling and the description of the Phase 4 commitments have been reviewed by Melinda Harris, Project Manager, and are acceptable. This reviewer has been requested to review the Safety Update and the sensitization study.

Safety Update

This Update covers the period from the last Update of November 27, 2003, to April 30, 2004.

Four serious adverse events, which were not considered by the sponsor to be drug related, have been reported in ongoing clinical trials, and one non-serious adverse event has been reported by Post-Marketing Surveillance. These are further described below.

To the best of the sponsor's knowledge, there have been no new publications that describe the clinical use of MAL-PDT beyond those included in previous submissions.

Seven clinical studies are ongoing, and one study, the sensitization

study, has been completed. Five of the studies are long term followup studies for the assessment of re-appearance of skin lesions treated with Metvix (the foreign trade name). The studies are summarized as follows.

Study description	Status	New safety information
RD.03.SPR29030: comparison of MetvixPDT with cryotherapy in actinic keratoses	11 patients	One unrelated SAE
*PC T309/00: comparison of MetvixPDT with cryotherapy and 5-FU in Bowen's disease	Ongoing followup	No new data
PC T313/03: MetvixPDT in immunocompromised organ transplant recipients with skin cancer	78 patients	One unrelated SAE
*PC T205/98: MetvixPDT in basal cell CA unsuitable to traditional therapy	Ongoing followup	Two new unrelated SAE's
*PC T303/99: comparison of MetvixPDT with excision in nodular basal cell Ca	Ongoing followup	No new data
*PC T304/99: comparison of MetvixPDT and cryotherapy in superficial basal cell Ca.	Ongoing followup	Narrative provided for previously reported SAE
*PC T310/00: MetvixPDT in high risk basal cell Ca.	Ongoing followup	No new data

*Data on these studies have been previously presented in the Safety Update of 11/27/03.

The one new serious adverse event which occurred in a patient treated for actinic keratoses was a myocardial infarction, which occurred 25 days after the last treatment with MetvixPDT.

Two new serious adverse events occurred in Study 205/98 on the long term followup of patients treated for basal cell carcinoma. These were deaths from ovarian cancer and from cardiovascular insufficiency, both occurring at about 4 years after the last treatment with MetvixPDT.

One new serious adverse event occurred in Study 313/03 on skin cancer in immunocompromised transplant recipients; this was a hospitalization of one weeks duration in a renal transplant patient in order to remove multiple progressive lesions.

Post-Marketing Surveillance has reported one new non-serious labeled phototoxic reaction. This was a 72 year old woman who was treated with MAL-PDT for actinic keratosis, and developed a severe phototoxic reaction on the same day. The sponsor considers this to be probably

related to the drug.

From initial marketing in 2001, — tubes of methyl aminolevulinate (MAL) cream 168 mg/g have been sold; the sponsor estimates that — patients have been treated with MAL-PDT.

Reviewer's evaluation: Other than one case of phototoxicity, there are no new adverse event reports which are drug related. Phototoxicity is currently cited as an adverse event in the draft labeling.

Study PC T112/03: Sensitization

A study report synopsis is provided on this sensitization study, performed in Norway on 21 subjects. The primary objective was to assess the sensitization potential of Metvix cream and its vehicle in patients who had received Metvix-PDT at least four times previously.

Applications of Metvix cream and its vehicle were randomly made to sites on the back for 48 hours. An assessment of the dermal response was made immediately and at 24 and 48 hours after removal of the patches. The occurrence of contact sensitization was recorded as negative, equivocal, or positive.

The results were that contact sensitization was observed at 3 sites treated with Metvix (14%) and at none of the sites treated with the vehicle. The sensitization reactions were associated with strong erythema with spreading, and other observations that included edema, vesiculation, papules, and glazing.

The sponsor's conclusion was that topical application of Metvix cream has the potential to cause contact sensitization in 14% of patients after prolonged (48 hours) exposure, but that the relevance of this to normal clinical practice is unclear.

Reviewer's evaluation: This study is not valid as a determination of the potential for contact sensitization. It lacks essential features of such a study, such as an adequate number of subjects, an induction period, rest period, and defined criteria for the assessment of sensitization.

Reviewer's summary and conclusions: Other than one adverse event that is already included in the current draft label, there are no adverse events reported in the Safety Update which are related to administration of methyl aminolevulinate cream. There is therefore no change in the safety profile of the drug from that previously reported.

The contact sensitization study PC T112/03 is not valid as a determinant of the potential for contact sensitization.

In conclusion, there is no information in the current submission which

would change the Approvable status of NDA 21-415, or alter the labeling for the product.

Phyllis A. Huene, M.D.

Cc: HFD-540/Wilkin
HFD-540/Luke
HFD-540/Huene
HFD-540/Vaughan
HFD-540/SLee
HFD-540/Harris

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

/s/

Phyllis Huene
6/21/04 09:59:34 AM
MEDICAL OFFICER

Markham Luke
6/22/04 10:27:58 AM
MEDICAL OFFICER

See also review by Mr. Richard Felton regarding device
issues and Approval recommendation. Concur with MO recommendation.
No additional change to labeling needed. Phase 4
commitment with timeline for submissions should be conveyed
in action letter..

Mr. Felton's review was not reviewed by Dr. Huene
at the time of closing her review. Sponsor
will need to address PPI informational need on
page 15 of the draft label sent with
the January AE letter.

Jonathan Wilkin
7/27/04 11:53:01 AM
MEDICAL OFFICER

See TL Summary Review Addendum of 7/27/04

Clinical Review of NDA 21-415 Response to Approvable Letter

APPLICATION NUMBER:

21-415

SUBMISSION/REVIEW DATES:

CDER STAMP DATE:

07/17/03

REVIEW COMPLETED:

01/13 /04

APPLICANT NAME:

Photocure ASA

ADDRESS

Hoffsveien 48

N-0377, Oslo

Norway

NAME OF COMPANY OFFICIAL
OR CONTACT PERSON

Dr. William A. Clementi, Pharm.D., F.C.P.

Clementi & Associates

919 Conestoga Road

Rosemont, PA 19010

610-581-7021; (Fax: 610-581-7025)

NOMENCLATURE

TRADENAME

Tradename ® Cream

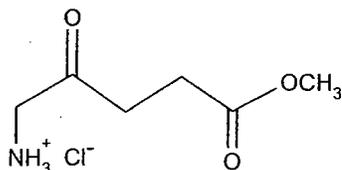
GENERIC NAME:

Methyl aminolevulinate hydrochloride

CHEMICAL NAME:

Methyl aminolevulinate hydrochloride

CHEMICAL STRUCTURE:



MOLECULAR FORMULARS:

 $C_6H_{11}NO_3 \cdot HCl$

MOLECULAR WEIGHT:

181.62

DOSAGE FORM:

Cream

ROUTE OF ADMINISTRATION:

Topical

REVIEWER: NAME:

Brenda Vaughan

TITLE:

Medical Officer

DIVISION:

Dermatologic and Dental Drug Product

DOCUMENTS REVIEWED:

NDA 21-415 Volumes 1 - 9

NDA 21-415 BM received 10-31-03

Table of Contents

Table of Contents.....		2
Executive Summary.....		4
I. Recommendations		
A. Recommendation on Approvability.....		4
B. Recommendation on Phase 4 Studies and/or Risk Management...4 Steps.....		4
II. Summary of Clinical Findings		
A. Brief Overview of Clinical Program.....		5
B. Efficacy.....		5
C. Safety.....		5
D. Dosing.....		6
E. Special Populations.....		6
Clinical Review		
I. Introduction and Background.....		7
A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups.....		7
B. State of Armamentarium for Indication(s).....		7
C. Important Milestones in Product Development.....		7
D. Other Relevant Information.....		7
E. Important Issues with Pharmacologically Related Agents.....		8
II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews.....		8
III. Human Pharmacokinetics and Pharmacodynamics.....		9
A. Pharmacokinetics.....		9
B. Pharmacodynamics.....		9
IV. Description of Clinical Data and Sources		
A. Overall Data.....		9
B. Tables Listing the Clinical Trials.....		9
C. Postmarketing Experience.....		10
D. Literature Review.....		10
V. Clinical Review Methods		
A. How the Review was Conducted.....		10
B. Overview of Materials Consulted in Review.....		11
C. Overview of Methods Used to Evaluate Data Quality and Integrity.....		11
D. Were Trials Conducted in Accordance with Accepted Ethical Standards.....		12
E. Evaluation of Financial Disclosure.....		12
VI. Integrated Review of Efficacy		
A. Brief Statement of Conclusions.....		12

	B. General Approach to Review of the Efficacy of the Drug.....	12
	C. Efficacy Conclusions.....	12
VII.	Integrated Review of Safety	
	A. Brief Statement of Conclusions.....	12
	B. Description of Patient Exposure.	12
	C. Methods and Specific Findings of Safety Review.....	13
	D. Adequacy of Safety Testing.....	15
	D. Safety Update.....	16
	F. Summary of Critical Safety Findings and Limitations of Data.	27
VIII.	Dosing, Regimen, and Administration Issues.....	27
IX.	Use in Special Populations.....	27
X.	Conclusions and Recommendations	
	A. Conclusions.....	27
	B. Recommendations.	30
XI	Appendix	31

CLINICAL REVIEW of NDA 21-415

Executive Summary Section

I. Recommendations

A. Recommendation on Approvability

1) An *Approval* recommendation is being made for NDA 21-415 for use of methylaminolevulinate-PDT in treatment of non-hyperkeratotic actinic keratosis (AK) of the face and scalp when used as supplementary to curettage in non-immunocompromised patients in the physician's office when other therapies are unacceptable or considered less appropriate. Approval as second line therapy is being recommended due to the high rate of sensitization of TRADENAME Cream and lack of retreatment and adequate long-term safety data. This application is for a drug-device combination and approval is contingent upon an approval recommendation from CDRH for the PhotoCure™ Halogen PDT Lamp (Model: CureLight 01).

B. Recommendation on Post-Marketing Studies and/or Risk Management Steps

The Applicant has adequately responded to the following issues that were identified in the September 19, 2002 Approvable Letter: 1) conducted a 21-day contact sensitization potential study of methyl-ALA, employing in the challenge phase test both methyl-ALA and ALA (which is an endogenous metabolite) to rule out cross-sensitization, 2) provided data driven instructions for prevention of sensitization of healthcare professionals handling TRADENAME cream, 3) developed visual instructional material as part of labeling to ensure the safe and effective use of the drug-device, and 4) modified the package insert to provide information for the practitioner addressing safety concerns and information needed for use of this drug product. The Applicant's response to additional information needed for the Package Insert and reviewer comments regarding adequacy of the Applicant's response are located in Appendix 1.

Based on review of the above, as a condition of approval the Applicant needs to agree to conduct a post-marketing safety study. The recommended long-term post-marketing safety study should be a 12-month safety study in at least 200 evaluable patients with 10 or more AK lesions with diameters of ≥ 4 mm, documenting the effects of retreatment of lesions with partial response and treatment of new lesions. Representative numbers of Asian and Hispanic heritage patients should be included in the study. Location of lesions should be sufficiently identified for long-term follow-up. The amount of MAL Cream (e.g., in grams, etc.) applied should be documented. Laboratory biochemical and hematological parameters should be collected during conduct of the post-marketing safety study.

Adverse events should be monitored and reported, including device related AEs, regardless of causality at all recurrence study visits. AEs occurring at or contiguous to the treatment site should be documented. The use of MedDRA terminology is recommended for describing adverse events. Use of local anesthetics and other methods for pain control (e.g., use of water spray, fans, etc.) should be documented.

Adverse event tabulation should be collected for each PDT treatment session to distinguish AEs due to lesion preparation, the drug alone, PDT, and possible incomplete photobleaching (e.g., increased burning after illumination associated with exposure to sunlight, etc.). These tabulations should include lesion preparation, pre-PDT (period of

time from application of MAL until illumination), peri-PDT (period during and shortly after illumination), and post-PDT (period from shortly after illumination to next application of MAL and/or end of follow up).

In lieu of conducting a separate post-marketing photoallergenicity study, monitoring for photoallergic skin reactions in the post-marketing study to distinguish phototoxicity from photoallergic reactions as to type and distribution (which may suggest causation) is acceptable. According to the Applicant (Approvable Response dated July 16, 2003), since UVA is an efficient activator of PpIX (Buchczyk et al 2001), it will be impossible to distinguish phototoxic reactions from photoallergenicity.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The current submission is a response to an Approvable Letter dated September 19, 2002.

B. Efficacy

Efficacy has been demonstrated in two, multicenter, blinded, randomized clinical trials with use of TRADENAME Cream-PDT over vehicle cream-PDT in treatment of non-hyperkeratotic actinic keratosis of the face and scalp when used as supplementary to curettage. No new efficacy data were submitted with the approvable response.

C. Safety

Additional safety data were submitted that supports approval; however, due to lack of retreatment data and high sensitization potential of TRADENAME Cream the safety database does not include enough information to exclude possible safety issues for use as first line therapy. Retreatment of lesions in partial response was not studied in the Phase 3 pivotal trials. Cross-sensitization of TRADENAME Cream with aminolevulinic acid (ALA), an endogenous substance although thought unlikely is suggestive (See Study PC T110/03) and is of concern.

In predisposed individuals, actinic keratosis is a chronic condition in which the number of lesions increases with advancing age; therefore, additional treatments are expected. Data provided by the Applicant are deficient regarding retreatment.

Data from the animal and clinical studies indicate that there is little potential for hepatotoxicity with topical application of TRADENAME Cream. However, these data may not be applicable to treatment of AK due to differences in lesion surface area may be greater in AK patients where lesions tend to be multiple. Since treatment related abnormalities have not been detected thus far, these data can be obtained in Phase 4 post-marketing study.

Safety data regarding overlapping fields or treatment of clustered lesions was not addressed during the clinical trials and it is unknown whether burns and ulceration of the treated lesions might occur. Treatment of multiple actinic keratosis lesions in one treatment session (e.g., multiple lamps vs. single lamp, staggering of lesions) has not been adequately addressed by the Applicant; however, can be obtained in Phase 4 post-marketing study.

The number of patients receiving local anesthetics is too small to make an accurate assessment. The effect of local anesthetics on safety and efficacy needs to be systematically studied and can be assessed in the post-marketing study. In the proposed label,

_____, this is recommendation is not supported by data from the clinical studies.

Due to differences in surface area of involvement, supporting biochemical and hematological laboratory parameters collected in BCC patients may not be applicable to patients with actinic keratoses. Overall, patients with BCC generally have fewer lesions and large BCC lesions were excluded from most studies except for Studies 203/98 and 310/00. Biochemical and hematological laboratory parameters were assessed in only 30 patients with actinic keratoses treated with the to-be-marketed concentration in Study 202/98 and laboratory parameters were obtained after only one treatment whereas the labeled regimen is for two treatments.

According to the Biopharm Reviewer, data submitted for PK Study 206/98, estimates that 1 gm (half-a-tube) was used on an average of 6 AK lesions in the first treatment session; however, a 10 mm perilesional application is included in the estimate vs. 5mm perilesional application as per the label. Based on estimates from this study, only up to 1 g per treatment session will be recommended for labeling (See Biopharm Review for details).

D. Dosing

According to the Biopharm reviewer, an intermediate concentration (between 80 and 160 mg/g applied for 3 h) may work as well. (See NDA 21-415 Biopharm review for details).

E. Special Populations (The review remains unchanged. See NDA 21-415 for details.)

I. Introduction and Background**A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups**

- Established Name: Methyl aminolevulinate hydrochloride
- Proposed Trade Name: Tradename® Cream
(note the Applicant has referred to this product as "Metvix" in early submissions, but this name was withdrawn)
- Sponsor's Proposed Indication: Non-hyperkeratotic Actinic Keratoses
- Proposed Dose/Regimen: (1) superficial preparation of the lesions followed by application of Tradename® 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 and total light dose of 75 J/cm² using the CureLight lamp.

B. State of Armamentarium for Indication(s)

Actinic keratoses (AKs) 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. Current therapies for AK include cryosurgery, electrodesiccation and curettage, topical application of 5-fluorouracil (5-FU), or recently approved photodynamic therapy with Levulan® Kerastick™ (aminolevulinate hydrochloride).

C. Important Milestones in Product DevelopmentRegulatory Background

Pre-IND Meeting, August 2, 1999
 Teleconference on Device Section, May 3, 2000
 End-of-Phase 2 Meeting, June 22, 2000
 Teleconference on Device Section, November 17, 2000
 Biopharmaceutical Teleconference, January 31, 2001
 Pre-NDA Meeting, May 2, 2001
 Approvable Action, September 19, 2002

D. Other Relevant Information

This application is a drug-device combination. The Applicant is studying use of TRADENAME Cream for treatment of basal cell carcinoma under NDA 21-576. NDA 21-576 cross-references NDA 21-415.

Applicability of Foreign Data to the U.S. Population and U.S. Medical Practice (See NDA 21-415)

As previously mentioned TRADENAME cream is approved in Europe. TRADENAME cream is approved for treatment of thin and non-pigmented AKs on the face and scalp when other therapies are considered less appropriate according to Summary of Product characteristics of foreign labeling submitted under NDA 21-576 (BZ) received May 12, 2003. A rationale for the second-line therapy indication was not provided.

E. Important Issues with Pharmacologically Related Agents

Aminolevulinic acid (ALA) is present in man and is present in both the mitochondria and cytoplasm of hemoglobin producing cells and in the liver. Tradename Cream (methyl aminolevulinic acid HCl) is an ester of ALA. A recently approved ALA drug product (Levulan®) is similar; however, does not contain a methyl group.

A provocative cumulative irritancy and sensitization (allergenicity) study with ALA cross-sensitization challenge was performed in 156 subjects (See Safety Studies). Of 98 subjects in the ALA cross-sensitization challenge phase, 2% (2/98) had equivocal reactions. Contrary to the Applicants assessment, cross sensitization to ALA (an endogenous substance) cannot be ruled out under conditions of this test (e.g., equivocal reactions, unblinded assessments, weak concentration of ALA, and unexplained positive reactions to the paraffin vehicle). Cross sensitization with endogenous ALA although thought to be unlikely is a concern.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**A. Chemistry** (The CMC Review has not been completed.)

PhotoCure submitted results where different gloves were tested according to the American Society for Testing and Materials (ASTM) standard method. In order for a glove to pass the test, the normalized breakthrough rate using an open-loop method, should be less than 0.1 $\mu\text{g}/\text{cm}^2/\text{min}$. Latex, polyvinyl chloride (PVC) and nitrile gloves were tested.

According to the submission, the permeation tests performed gave the normalized breakthrough time and the maximum permeation steady state. Methyl aminolevulinic acid Cream (Batch No. 0275U) was used in the tests. Of the medical gloves tested, a thick latex glove (0.20 mm / 8 mils) and a nitrile glove (0.13 mm / 5 mils) passed the ASTM F 739-99a test. The maximum permeation rate obtained was well below the test requirements. A thinner latex glove and two vinyl gloves were also tested. However, for these gloves the normalized breakthrough rate of 0.1 $\mu\text{g}/\text{cm}^2/\text{min}$ was obtained after 3-5 minutes, reaching a maximum steady state permeation rate of 0.14-0.15 $\mu\text{g}/\text{cm}^2/\text{min}$. This maximum rate is only slightly above the limit of 0.1 $\mu\text{g}/\text{cm}^2/\text{min}$ set in the standard.

Reviewer's comment:

According to the Chemistry review, only the nitrile gloves provide adequate protection from contact with TRADENAME Cream (See chemistry review for details).

B. Animal Pharmacology and Toxicology (See Pharm/Tox Review for details)

The Pharm/Tox Reviewer recommends that from a pharmacology/toxicology standpoint, the application is approvable.

C. Biopharmaceutics

See Biopharm review for details of the PK studies. The Biopharm recommendation is that the Sponsor's proposal to conduct a Phase 4 study as per request of the Agency in the Clinical Pharmacology and Biopharmaceutics section is acceptable. The synopsis of the study appears to meet the purpose of the study; however, the complete protocol should

include the amount of methyl ALA (number of tubes and amount used from each tube) used as well as surface area used for each patient.

Two new PK studies were submitted. Results of Study PC T212/00 were requested by the Agency for inclusion in the safety database. The primary objective was to compare the local phototoxic response following PDT with TRADENAME Cream and PDT with ALA in psoralen cream in healthy volunteers.

Study PC T214/01 the primary objective is to establish the kinetics of the photoactive porphyrins that accumulate following application of MAL cream to normal skin.

Secondary objectives are to determine the phototoxic potential of residual photoactive porphyrins at various timepoints following MAL cream application and light exposure, and to report any adverse events.

D. Statistics

No statistical issues are identified.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics (See original NDA review.)

B. Pharmacodynamics

Study PC T110/03, an irritancy/allergic sensitization potential dermal safety study, was conducted 156 normal human volunteers. The results are discussed in Dermal Safety Studies Section.

IV. Description of Clinical Data and Sources

A. Overall Data

This review is based on data submitted by the Applicant.

B. Tables Listing the Clinical Trials

Three new clinical studies were submitted and are listed in Table 1.

Table 1: Clinical Studies

Study Number	Location	Population Studied	Study Objective	Location of Clinical Trial Report
PC T214/01	Norway	16 Healthy Volunteers	Primary objective is to establish the kinetics of the photoactive porphyrins that accumulate following application of MAL cream to normal skin. Secondary objectives are to determine the phototoxic potential of residual photoactive porphyrins at various timepoints following MAL cream application and light exposure, and to report any adverse events.	Section 3 (summary) and Attachment 1 (study report). Included in NDA 21-576

PC T110/03	UK	156 Healthy Volunteers	The primary object is to assess the sensitization potential of TRADENAME 160 mg/g Cream and the corresponding vehicle. The secondary objects are to assess the following: <ul style="list-style-type: none"> • Presence of cross-sensitization to 5-aminolevulinic acid (ALA) and the corresponding vehicle skin irritation caused by Tradename 160 mg/g Cream and the corresponding vehicle.	Vol. 5 of 9, page 1
PC T212/00	Germany	34 Healthy Volunteers	The primary objective was to compare the local phototoxic response following PDT with Tradename Cream and PDT with ALA in psoralen cream in healthy volunteers.	Vol. 9 of 9, page 1

C. Post-Marketing

According to the Applicant (under NDA 21-576) on June 15, 2001, PhotoCure received the first marketing approval for methyl aminolevulinic acid cream 168 mg/g-photodynamic therapy (PDT) for the treatment of actinic keratosis (AK) and "high-risk basal cell carcinoma" (HR-BCC) in Sweden. As of October 16, 2002, commercial sales data show that approximately 100 tubes of methyl aminolevulinic acid cream 168 mg/g have been sold (after approval) in Sweden, Norway, Denmark, and Finland.

According to the submission (Vol. 1, pg. 108), TRADENAME Cream is currently approved for treatment of AK and/or BCC in 15 countries and is marketed in 6 of these (Sweden, Norway, Denmark, Finland, Germany, and United Kingdom). The total number of TRADENAME tubes sold from September 2001 until mid June 2003 was 100 tubes.

During this period there has been one spontaneous report of challenge positive sensitization to TRADENAME-PDT in one 30-year old female patient from Copenhagen suffering from Necrobiosis lipoidica of her lower legs after three PDT treatments with TRADENAME Cream. Two serious European post marketing AEs involving serious erythema and facial edema after treatment for scalp AKs were also reported.

D. Literature Review

The articles submitted did not appear to relate to TRADENAME Cream safety data.

V. Clinical Review Methods

A. How the Review Was Conducted

Adequacy of the Applicant's responses to the the Approvable letter dated September 19, 2002 and supportive data are the subject of this Approvable Response review.

It was determined that prior to approval of TRADENAME Cream-PDT for treatment of nonhyperkeratotic AKs, data were needed to support safe use of the product and modifications to the label were recommended (See Appendix 1). Safety issues to be addressed by the Applicant included submission of biochemistry and hematological laboratory data, conducting a contact sensitization and cross-sensitization potential study of TRADENAME Cream, providing Universal Precautions procedures for use of the device, and providing non-promotional visual instructional material (e.g., video, CD, etc.) as part of labeling, to ensure safe and effective use of the drug-device. A Safety Update was also requested.

As a Phase 4 commitment, the following Phase 4 post-marketing studies were requested:

- A. A clinical 12-month study in at least 200 evaluable patients with 10 or more lesions (located on the face and scalp) in whom the following are collected: hepatic transaminases (ALT and AST), alkaline phosphatase, total bilirubin, and complete blood count plus differential data both at baseline and at one week after the second repeat dose 7-day regimen.
- B. A longer-term clinical study documenting the effects of multiple retreatments and recurrence rate with this product. Actinic keratoses may be considered to be a chronic intermittent disease and multiple retreatments are common, especially in older, sun-overexposed patients.
- C. A clinical dermal safety study to determine the photoallergenicity potential of TRADENAME Cream with a diluted form of TRADENAME Cream.
- D. A safety and efficacy Phase 4 study of TRADENAME Cream in patients of Asian and in patients of Hispanic heritage.

The Applicant addressed all approvable issues. The Applicant is willing to conduct one Phase 4 study in at least 200 evaluable patients with 10 or more lesions located on the face and scalp; however, the Applicant proposes not to measure laboratory parameters during Phase 4. The protocol synopsis is located in Volume 1 (pg. 147).

According to the submission (Vol. 1, pg. 146), the Applicant cannot agree (for scientific reasons) to determine the photoallergenicity potential of TRADENAME Cream with a diluted form of TRADENAME Cream. According to the submission, since UVA is an efficient activator of PpIX (Buchczyk et al 2001), it will be impossible to distinguish phototoxic reactions from photoallergenicity. Instead the Applicant proposes monitoring allergic skin reactions in the Phase 4 study as to type and distribution which may suggest causation.

B. Overview of Materials Consulted in Review

Materials reviewed include:

NDA 21-415 Vol. 1-9, User Manual PhotoCure™ Halogen PDT Lamp CureLight BroadBand CE 0470 (Version 2.1), Medical Officer's Review of NDA 21-576, and PhotoCure ASA's Dermatologic & Ophthalmic Drugs and Advisory Committee Briefing Document (dated September 10, 2003).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits were performed for this submission.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the submission (Vol. 14.5, pg. 10), Study PC T110/03 was conducted in accordance with the ethical principles of the Declaration of Helsinki.

E. Evaluation of Financial Disclosure

None submitted.

VI. Integrated Review of Efficacy**A. Brief Statement of Conclusions**

No new efficacy studies were submitted; therefore, refer to original NDA 21-415 for the efficacy details.

VII. Integrated Review of Safety**A. Brief Statement of Conclusions**

An *Approval* recommendation is being made for NDA 21-415 for use of methyl-aminolevulinate-PDT in treatment of non-hyperkeratotic actinic keratosis (AK) of the face and scalp when used as supplementary to curettage in non-immunocompromised patients in the physician's office when other therapies are unacceptable or considered less appropriate. Approval as second line therapy is being recommended due to the high rate of sensitization of TRADENAME Cream and lack of retreatment and adequate long-term safety data. This application is for a drug-device combination and approval is contingent upon an approval recommendation from CDRH for the PhotoCure™ Halogen PDT Lamp (Model: CureLight 01).

In predisposed individuals, actinic keratosis is a chronic condition in which the number of lesions increases with advancing age; therefore, additional treatments can be expected. Risk management provided by the Applicant is deficient regarding safety of retreatment and adequate long term safety data were provided. Adequate risk management with repeated use of TRADENAME Cream is needed for this drug product that exhibits such an extraordinarily high contact sensitization potential.

B. Description of Patient Exposure

The amount of drug product applied was not provided or addressed by the Applicant in the study report, case report forms, data listings, nor in the Integrated Summary of Safety. According to the Applicant, the amount of cream applied was dependent upon the number and size of AK lesions; however, the Applicant failed to provide adequate documentation of the amount of TRADENAME Cream used. The Applicant provided the number of tubes used per treatment session (Vol. 1, pg. 89); however, this reporting method is not credible unless all returned tubes of MAL cream were empty. For example, the following patients were listed as using 1 tube (2 g); however, it not logical that these patients had the same amount (1 tube) of study drug applied:

- Pt. 2008 with 3 lesions measuring 5, 7, and 11mm
- Pt. 2004 with 4 lesions measuring 5, 7, 7, & 6 mm
- Pt. 2039 with one 5mm lesion
- Pt. 4011 with one 9mm lesion

The Applicant is recommending use of no more than _____ of product be used for each of the two weekly treatment sessions. Data was only submitted for Study PC T305/99 (Attachment 4, Vol. 3 of 9). Only 10% (9/87) of patients treated in Session 1 and 8% (6/87) of patients in Session 2 may have used 6 gram use per treatment session. These numbers are too small to adequately assess safety and efficacy of this level of exposure. According to the Statistical Review (NDA 21-415, page 7 of 36), more than 60% of patients in Study 305 had less than 4 lesions at baseline.

Table 2: Amount of TRADENANE Cream Applied (Study PC T305/99)

No. of Tubes Used Per Treatment (grams)	Treatment 1 % Patients (N = 87)	Treatment 2 % Patients (N = 76)
1 (2 gm)	55% (48)	56% (43)
2 (4 gm)	25% (22)	26% (20)
3 (6 gm)	10% (9)	8% (6)
4 (8 gm)	3% (3)	4% (3)
5 (10 gm)	2% (2)	1% (1)
6 (12 gm)	3% (3)	4% (3)

Review comments:

Data provided on the number of tubes dispensed is not reliable; the Biopharm Reviewer estimates that 1g (half-a-tube) was used on an average of 6 AK lesions in the first treatment session based on data submitted from Study 206/98. Use of up to 1g per treatment session is recommended for labeling based on estimates from Study 206. This data mirrors use in the Phase 3 studies since a majority of patients in the Phase 3 studies had 6 or less lesions (See Biopharm Review for details).

C. Methods and Specific Findings of Safety Review

All adverse events were classified as local or non-local. According to the Applicant (NDA 21-576), local refers to skin and appendages; however, this definition is somewhat complicated in that it may be construed as referring to the treatment site. For example, the Applicant reported tingling skin and application site reaction as “non-local” adverse events (NDA 21-415, Vol. 37 of 68, pg. 58).

Reviewer comments:

The use of MedDRA terminology is recommended for describing adverse events.

Local Safety

The Applicant submitted other adverse reactions tabulations; however, the following table is most relevant and is included in the label. The Applicant submitted the following table in response to the request to calculate percentages for adverse reactions based on occurrence(s) per patients.

Table 4: Percentage of Patients with Local Adverse Reactions

Percentage of patients with local adverse reactions based on occurrence per patient in vehicle controlled phase 3 studies.		
Events	TRADENAME-PDT (n=130)	Vehicle PDT* (n=61)

	% of patients with AEs	% of patients with AEs
Burning sensation skin	50.0%	14.8%
Erythema	46.2%	19.7%
Pain skin	20.8%	9.8%
Stinging skin	19.2%	3.3%
Crusting	15.4%	9.8%
Oedema skin	15.4%	1.6%
Skin peeling	10.8%	3.3%
Blisters	10.8%	3.3%
Bleeding skin	8.5%	3.3%
Pruritus	6.2%	3.3%
Itching	6.9%	0%
Skin ulceration	5.4%	0%
Skin infection	2.3%	1.6%
Rosacea	0%	0%
Skin hyper-pigmentation	0.8%	0%
Skin disorder	0%	1.6%
Hyperkeratosis	0%	1.6%

Reviewer comments:

Pruritus and itching should be combined in the AE table. Table 4 above, Percentage of Patients with Local Adverse Reactions, was modified and included in the label (See Attached Label Review).

Anesthetic and/or analgesic use

It is the opinion of this reviewer that most physicians would choose to anesthetize prior to curettage. Use of local anesthetic has been discouraged during clinical development thus safety and efficacy data are limited. The Applicant did not provide a rationale for discouraging anesthetic use during clinical development for a procedure associated with significant pain and burning (e.g., curettage and phototoxic reactions).

Systemic Safety Profile (Non-Local)**Laboratory Monitoring**

According to the Applicant, blood counts and biochemistry were examined in 375 patients in Studies 101/97 (16 patients with BCC), 202/98 (dose-ranging study in 112 patients with AK; however, only 30 patients were treated at the labeled concentration), 203/98 (141 BCC patients), 204/98 (12 patients enrolled in an exploratory split-face application study vs. Efudex), and 205/98 (94 BCC patients). There were no comparator study arms in any of the studies and no retreatment evaluations were included in the safety database.

The following parameters were measured in all the studies: hemoglobin, ALT, AST, and bilirubin. The following additional laboratory parameters were measured in certain studies: Study 101/97 – platelets, leukocytes, erythrocyte sedimentation rate, creatinine, ALP, GGT, sodium, and potassium; Study 204/98 – creatinine, WBC, and thrombocytes; Study 205/98 – creatinine, platelets, and WBC; and Studies 202/98 and 203/98 included WBC and thrombocytes.

In the AK Study 202/98 and BCC Study 205/98, patients received only a single treatment, study drug concentration and application times varied. In Study 205/98, 78 patients with BCC were treated with two treatment sessions per cycle; however, typically BCC patients have fewer lesions and thus less surface area of exposure to TRADENAME Cream. No treatment related laboratory abnormalities were noted in the studies as conducted. However, assessment of laboratory parameters should be obtained under maximal use conditions in patients with AKs since lesions can be numerous.

D. Adequacy of Safety Testing

The Applicant did not provide retreatment safety and efficacy data and the reliability of the recurrence data is questionable. The Applicant provided the number of tubes dispensed in this approval response. However to provide a general guide for clinical use, the following should have been considered for each patient: the number of lesions treated, approximate surface area of each application site, approximate total surface area of application, number of tubes used, and number of grams used from each tube.

Drug exposure data from PK Studies 101/97, 206/98, and 214/01 were submitted. Study 101/97 was conducted in 7 BCC patients with 7 lesions and Study 214/01 was conducted in 16 healthy human volunteers at the labeled concentration. At the labeled concentration in Study 206/98, it is estimated that 1 gm (half-a-tube) was used on an average of 6 AK lesions in the first treatment session; therefore, up to 1 gm per treatment session will be recommended for labeling (See Biopharm Review for details). No biochemical or hematological laboratory parameters were collected in these studies.

Data from the animal and clinical studies submitted indicate that there is little potential for hepatotoxicity with topical application of TRADENAME Cream. However, these data may not be applicable to treatment of AK due to greater lesion surface area involvement in AK patients where lesions tend to be multiple. Since treatment related abnormalities have not been detected thus far, these data can be obtained in Phase 4 post-marketing study.

Safety data regarding overlapping fields or treatment of clustered lesions was not addressed during the clinical trials and it is unknown whether burns and ulceration of the treated lesions might occur. Treatment of multiple actinic keratosis lesions in one treatment session (e.g., multiple lamps vs. single lamp, staggering of lesions) has not been adequately addressed by the Applicant; however, can be obtained in Phase 4 post-marketing study.

The number of patients receiving local anesthetics is too small to make an accurate assessment. The effect of local anesthetics on safety and efficacy needs to be systematically studied and can be assessed in the post-marketing study.

Safety Update

Initially, a Safety-update had not been submitted to the NDA since the approvable action dated September 19, 2002. Two serious AEs and expected post marketing cases of

serious erythema and facial edema two patients treated for AKs were reported in the Advisory Committee Briefing Package (dated September 10, 2003) that are not included in the 120-day update for the BCC indication under NDA 21-576. It is unclear why serious facial edema (one requiring hospitalization) following treatment of AKs located on the scalp is considered expected versus unexpected. Post-marketing reports of dizziness, hair loss, light sensitivity, and blurred vision were included.

Additional adverse events of concern are reported instances of patients who have developed squamous cell and basal cell carcinoma at the site of treatment. The relationship between these adverse events and photodynamic therapy with TRADENAME Cream is not clear at this time. In open-labeled BCC studies, two reports of urticaria were reported with one considered possibly related and the other with an uncertain relationship to study treatment. Contact urticaria versus immunologically mediated urticaria needs to be determined.

A Safety Update was received December 03, 2003; however, did not include those ADRs reported in the September 10, 2002 Advisory Committee Briefing Document. Subsequently, a fax submitted to NDA 21-415, Ser. #59 was received from the Applicant on December 12, 2003 that includes an updated Section 2.3 "Adverse Events Reported After Market Introduction". According to the Applicant, additional cases from the Briefing Document/Periodic Safety Update and new case presented are not considered to impact the overall safety profile for MAL-PDT.

Reviewer comment:

The current Safety Update appears acceptable.

Between Patient Sterilization of the Device

The Applicant is proposing use of "snap on" disposable plastic sleeve on the underside of the horseshoe-positioning device and the light-measuring probe Vol. 1, pg. 137). Although considered a device issue, data to support Universal Precautions method proposed by the Applicant for use of the device safe that does not hinder efficacious use has not been submitted (See CDRH Review); therefore, the issue remains unresolved.

Long-term safety data

Data from study PC T 202/98, an open exploratory (Phase I/II) study of Tradename Cream 80 mg/g and 160 mg/g applied for 1 or 3 hours in patients with primary AKs, was submitted. Recurrence was assessed at month 12 in all lesions that had shown complete response in the previous evaluation. It is not clear how lesion identification was ascertained at the 9 or 12-month follow-up; therefore, these data are not reliable.

Safety Studies Submitted

Three new studies (one topical safety and two PK studies were submitted). These studies are reviewed for safety. (See Biopharm review for details of Studies 214/01 and 212/00.)

Dermal Safety Studies**Study PC T110/03**

Titled: "A Double-Blind, Randomized, Phase 1 Repeated Insult Patch Study To Assess The Sensitization Potential Of Metvix® 160 Mg/G Cream, Its Vehicle, And Aminolevulinic Acid And Its Vehicle In Healthy Subjects"

Study dates:

First subject entered: February 25, 2003

Study completion date: April 22, 2003

Primary Objective

The primary object was to assess the sensitization potential of Metvix® 160 mg/g Cream and the corresponding vehicle.

Secondary Objectives

The secondary objects were to assess the following:

- presence of cross-sensitization to 5-aminolevulinic acid (ALA) and the corresponding vehicle
- skin irritation caused by TRADENAME 160 mg/g Cream and the corresponding vehicle.

Study Design

The study was a single center, double blind, within-subject, randomized, study conducted in healthy volunteers, assessing the sensitization by TRADENAME 160 mg/g Cream and the corresponding vehicle and cross-sensitization to ALA and its vehicle. Following a run in period (screening) of one week, the study duration was six weeks. Two hundred-fifteen (215) subjects were to be included in the study.

The study was divided into the following three sequential periods:

Induction phase:

Application under occlusion of TRADENAME 160 mg/g cream and its vehicle, to the same skin sites 3 times weekly (Monday, Wednesday, Friday) for 3 weeks, for a total of 9 cumulative doses. Scoring performed at each patch removal.

Rest Phase: The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

Challenge Phase: TRADENAME Cream, its vehicle, ALA and ALA-vehicle patches were to be applied to new skin sites for 48 hours with scoring performed at 30 minutes, 24 and 48 hours after patch removal.

Amendment 1 (dated 04.02.03)

Nature of the revised amendment was predominately administrative in nature; however, notable changes are:

- Change in ALA vehicle from ethanol 48 % (v/v) to yellow soft paraffin. Ethanol is vasodilating and skin irritating in high concentrations.

- It was considered necessary to specify the application sites for TRADENAME / placebo and ALA / vehicle in the challenge phase. It was decided to place TRADENAME / placebo above ALA / vehicle on the upper arms in each subject in the challenge phase.

Reviewer's comment: *Study blind only applied to each active vs. its vehicle (TRADENAME Cream vs. ALA was not blinded). The rationale for specifying the location of Metvix / placebo above ALA / vehicle on the upper arms in each subject in the challenge phase was not provided.*

Amendment 2 (dated April 2, 2003)

Nature of the Amendment

To describe changes in study procedures according to study results seen at the 17th of March.

Rationale for the Amendment

At the 17th of March 2003, approximately half of the first cohort of 102 subjects had developed cutaneous reactions at one of the two test sites at visit 6 or 7. The time course of these reactions and their clinical appearance suggest the development of sensitization. As a result it has been decided that:

- 1) The number of patients with cutaneous reactions indicate that it is not necessary to expose more subjects, therefore the last 65 subjects that had been screened were not entered into the active phase of the study.
- 2) From the 18th of March, if a significant cutaneous reaction occurs at a treated site then that product will not be reapplied to a fresh site during the induction phase as originally stated in the protocol.
- 3) If a subject agrees a challenge will be carried out in order to confirm sensitization and to check for cross reactivity to ALA itself. Also if the subject agrees to participate in the challenge phase, the subject will be asked to have one application of only 3 hours to check for sensitization reactions after the application time that is used clinically.

Study Duration

The total number of visits for the induction phase is ten, over a period of twenty-two days with a 14 day treatment free period followed by a 48 hour treatment and a 30 minutes, 24 hour and 48 hour post removal of the patches assessment visits. The entire duration of the study will be fourteen visits over a period of forty days. Visits are to occur at Screening/Treatment 1, Treatments 2 through 9, Final Induction Phase Visit, Challenge Treatment, Assessment 1, Assessment 2 and Assessment 3.

Randomization and Blinding

MAL cream and the vehicle were of identical appearance. ALA and its vehicle were identical in appearance. Study medications was labeled with the subject number and tube "LEFT" or "RIGHT" corresponding to the randomization list.

Reviewer comment:

According to Amendment, the location of Metvix / placebo was to be placed above ALA / vehicle on the upper arms in each subject in the challenge phase. Determination of cross-sensitization was also an objective of this study; therefore, blinding to MAL and ALA should have been incorporated in the protocol to obtain an unbiased determination.

Description of Investigational Drug

Metvix 160 mg/g cream and its vehicle was supplied in 2 gram collapsible tubes. The investigator will be provided a sufficient amount of cream for the duration of the study, which is a total of 1600 tubes (800 tubes of each test cream). The strength of Metvix 160 mg/g cream is given as the concentration of the active entity, methyl 5-aminolevulinate, which is present as the hydrochloride (P-1202).

Vehicle cream will be similar in appearance and consistency to the active cream. It will contain the same excipients, with the addition of paraffin wax and yellow iron oxide (E172), but without the active ingredient. The paraffin wax and yellow iron oxide (E172) will be added for blinding purposes; these ingredients will allow the vehicle cream to have the same appearance (viscosity and color) as the Metvix cream. Penn Pharmaceuticals, UK, manufactured Metvix 160 mg/g cream and its vehicle.

ALA 1 mg/ml (0.1%) in soft yellow paraffin and paraffin vehicle were used in the challenge phase. ————— produced ALA 0.1% ointment and vehicle that were to be used on the day of production.

Inclusion Criteria

The following inclusion criteria must be confirmed prior to subject enrolment:

- Males or females above 18 years of age
- Normal and healthy as confirmed by medical history
- Able and willing to follow the protocol for the duration of the study
- Written informed consent

Exclusion Criteria

A subject that is ineligible for inclusion is a subject fulfilling any of the following criteria:

- Evidence of cutaneous disease of the back
- Subjects immunosuppressed for idiopathic, disease specific, or therapeutic reasons.
- Use of systemic corticosteroids or the use of topical corticosteroids on the back within the past 2 weeks
- Use of topical retinoids or alpha-hydroxy acids or systemic retinoids, chemotherapy or immunotherapy within the past 4 weeks
- Known allergy to Metvix, a similar PDT compound or excipients of the cream.
- Subjects with history of hypersensitivity to nut products.
- Participation in other clinical studies either currently or within the last 30 days.
- Pregnant or breast-feeding: All women of child-bearing potential must use adequate contraception (e.g. barrier methods, oral contraceptives or intrauterine device) during the treatment period and one month thereafter. In addition, they must have a negative pregnancy test prior to treatment.
- Subjects currently receiving regular UV therapy or subjects that sunbathe on a regular basis

Study Procedures

Cream Application and Irritation/Sensitization Assessments (Visits 1 through 9)

Visit 1 (Initiation of Cream Application)

One medicated patch of Metvix 160 mg/g cream was applied to designated areas of each subject's lower right and left sides of the back (a total of two patches on each subject's back). The Finn chamber with approximately 0.1 g or 0.1 ml of a cream, was applied to the subject's back and affixed with Scanpor. The chambers were also covered with a light opaque material. The patch should be left in place, dry, protected from light and undisturbed for 48 hours.

Visits 2 – 9 (Assessment of Irritation and Cream Application)

For medicated patches applied on days Monday and Wednesday, subjects will return 48 hours after the patches were applied. Subjects whose patches were applied on a Friday, will return 72 hours after the application of the medicated patches. Patch removal with local irritation assessment after 10 minutes according to the following eight-point scale.

Erythema (irritation score)

At each assessment time the sites will be graded for erythema on a eight ranking scale, as follows:

- 0 = No reaction.
- 0.5 = Slight, patchy erythema.
- 1 = Slight uniform erythema.
- 2 = Moderate, uniform erythema.
- 3 = Strong erythema.
- 4 = Strong erythema, spreading outside patch.
- 5 = Strong erythema, spreading outside patch with either swelling or vesiculation.
- 6 = Severe reaction with erosion.

Clinical observations

If in addition to erythema other clinical signs of cutaneous irritation are present these will be recorded in the case record form as follows:

- OE = Oedema
- V = Vesiculation
- S = Scaling
- C = Cracking or crazing
- SC = Scabbing
- P = Papules
- SO = Reaction spreading outside area of application
- G = Glazing

Any other subjective observation such as burning or stinging will be recorded as an adverse event in the CRF. At each visit the adhesion of the patches will be recorded before removal using a five point ranking scale.

After the scores of the treated sites have been recorded, two new medicated patches (one medicated patch for each tube, 'left' and 'right') were applied to the same appropriate, previously treated areas of the back. This entire process will be repeated for a cumulative total of 9 doses over a 22-day period.

If any site on a subject's back attains an erythema score of '3' or greater during the induction phase (the first 9 applications), that site should no longer receive treatment. However, the next patch may be placed to an adjacent, previously untreated site. If a reaction score of '3' or greater occurs at the new site, no further induction applications should be made. Subjects who receive an erythema score of 2 or greater the first week of the induction phase, will not be included in the challenge phase of the study.

Visit 10 (Final Induction Phase Visit)

At Visit 10 (72 hrs after the 9th treatment), the final two patches will be removed and scored as previously. Subjects did not receive treatment for the next 14 days.

Visit 11 (Challenge Treatment)

Fourteen days after visit 10, subjects returned for a challenge treatment of each of the creams in tubes 'left' and 'right' and ALA solution and its vehicle labeled left and right. As for the induction phase, the Finn chamber was loaded with approximately 0.1 g of a cream or 0.1 ml of solution and then applied to each subject's upper arm. The allocation of Metvix and its vehicle to the left and right side was to be the same as in the induction phase. There was a separate randomization list for ALA and ALA-vehicle, with regards to application to the left or right arm in separate sites from the ones treated with Metvix and its vehicle. The chambers were affixed to the outside of the upper arm with Scanpor tape and covered with light opaque material. Scanpor tape may be used, as needed, for extra adhesion. The patches for this challenge application should be applied to the outside of the upper arm. Once applied, the patches should be left in place, dry, protected from light and undisturbed for 48 hours.

Visit 12 (Assessment 1 – 48 Hours and 30 Minutes After Visit 11)

Subjects returned 48 hours after Visit 11. Challenge patches were removed and sites were assessed and scored 30 minutes later. Test sites were then covered by a 12 mm Finn chamber, affixed to the patients arms with Scanpore tape and covered with light occlusive material.

Visit 13 (Assessment 2 – 24 Hours After Visit 12)

Twenty-four hours after the removal of the patches, the subjects returned for an assessment of the four treated sites, and sites were scored. The test sites were covered by a 12 mm Finn chamber, affixed to the patients arms with Scanpore tape and covered with light occlusive material.

Visit 14 (Assessment 3 – 48 Hours After Visit 12)

Forty-eight hours after the removal of the patches, the subjects returned for their third assessment of the four treated sites, and scored as previously.

A narrative description of each reaction in the challenge phase was given, together with the opinion of the investigator as to whether any reactions seen at the test site are felt to be indicative of contact sensitization. The contact sensitization score was recorded only once at visit 14.

The opinion will be recorded as

0 = Negative (no allergy).

1 = Equivocal.

2 = Positive (allergic contact dermatitis).

Reviewer comments:

Descriptors for negative, equivocal, and positive should have been provided.

Assessment of Safety**Serious Adverse Event****Definition Serious Adverse Event**

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life threatening,
- requires hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect.

Statistical Evaluation**Statistical analysis**

The statistical analysis was the responsibility of —
Tabulation of summary statistics and data analysis will be performed using SAS software version 6.12 or later. Since this is a safety study the statistical analysis is descriptive. Thus, statistical tests are to be regarded as descriptive rather than confirmatory. All subjects will be presented in separate listings.

Disposition of Subjects

All subjects included into the study will be considered in the statistical analysis.

Safety

The primary safety endpoint is the proportion of subjects in each of the three categories of the contact sensitization score at the end of challenge phase displayed by the four treatments Metvix, it's vehicle, ALA and ALA-vehicle. A frequency tables will be used to summarize the number and percentage of subjects in each category of the three-point contact sensitization scale by treatment. The 95% confidence intervals for the proportion of the subjects in each category of the score stratified by treatment will be calculated using the method of Clopper and Pearson.

Secondary safety end points are the proportion of subjects stratified by the two treatments Metvix and it's vehicle in each erythema score category, based on an eight-point dermal response scale, during the 21 day induction phase and the 48 hours challenge phase. In addition, the mean cumulative irritation score and the total cumulative irritation score will be analyzed for both phases and total. The individual total cumulative irritation score will be calculated for each subject and for each visit as the sum of his/her scores up to and including this visit per treatment for both phases and combined. The individual mean cumulative irritation score will be calculated

Study Results

One hundred fifty-six (156) subjects were tested. Sixty-eight subjects were screened; however, did not receive Metvix®/vehicle due to development of cutaneous reactions at one of the two test sites at visit 6 or 7 in the first cohort of 102 subjects. According to

(See Amendment 2, the time course of these reactions and their clinical appearance suggest the development of sensitization. Of the 156 subjects, 13 (15%) were male and 133 (85%) were females with age ranging from 18 to 72 years (mean 42 years).

Sixty (60) subjects were withdrawn:

- 25 subjects due to skin reaction during the induction phase,
- 33 due to consent withdrawal (according to Vol. 5, page 28) due most likely due to skin reactions during induction),
- 1 (Patient #4) due to an unrelated SAE
- 1 (Patient # 135) for other reasons (Listed as Investigator decision according to Vol. 6, page 30); however, no rationale was provided.

During the challenge phase 58 subjects were exposed for 48 hours to MAL Cream and ALA (1 mg/g) and respective vehicles. There were 40 subjects who received ALA and its vehicle only (a total of 98 subjects with ALA and its vehicle applied). Four patients were challenged with MAL/MAL vehicle for 3-hours.

Of the four patients challenged with MAL/MAL vehicle for 3-hours, no clinical observation recorded following the challenge phase for the active site; however, faint erythema (score of 0.5) was recorded for the vehicle site for subject 140. For ALA, one clinical observation of papules was made at Visit 14 for Subject 146.

Table 5: (Sponsor's Table V, Vol. 5, pg. 30) Challenge Phase. Number and Proportion of Subjects in the Contact Sensitization score by Compound

Compound	Number of Subjects	Contact Sensitization Score							
		Missing		Negative (0)		Equivocal (1)		Positive (2)	
		N	%	N	%	N	%	N	%
MAL	58	1	2	24	41	3	5	30	52
MAL Vehicle	58	1	2	55	95	1	2	1	2
ALA	98	2	2	94	96	2	2	0	0
ALA Vehicle	98	2	2	94	96	0	0	2	2

Sponsor's Data Source: Tables 14, 15

Fifty-two percent (52%) of the subjects (30/58), who agreed to challenge with MAL cream, were positive (sensitized). Forty subjects refused challenge with MAL cream and there were 60 dropouts. At least 58 of the 60 subjects, who withdrew from the study, discontinued due to irritation/sensitization; therefore, the sensitization rate is higher.

Cross Sensitization

Cross-sensitization challenge consisted of 156 subjects. Four subjects had questionable reactions to ALA or its vehicle (Subjects 15, 24, 39 & 146). Subject 146 developed papules at Visit 14 with a sensitization score of 0 (negative). Sensitization scoring for cross-sensitization follows:

0 = Negative (no allergy)

1 = Equivocal

2 = Positive (allergic contact dermatitis)

Table 6: ALA Cross-Sensitization Positive/Equivocal Subjects

Subject #	MAL Score	MAL-VEH Score	ALA Score	ALA-VEH Score
#15	2	0	1	0
#24	2	1	1	2
#39	2	2	0	2

The cross-sensitization to the paraffin vehicle is unexpected. The results are not reliable in that this cross-sensitization portion of the test was not blinded to MAL vs. ALA; none-the-less, equivocal results were noted indicating possible sensitization to ALA.

Reviewer comment:

The potential of MAL cream to induce contact sensitization in the intended population with an impaired epidermal barrier (e.g., lesion preparation with a sharp dermal curette) are unknown; however, are expected to be higher than in normal skin.

Reviewer Conclusion

MAL cream is a potent contact sensitizer with a sensitization rate of probably greater than 52% in human volunteers with intact epidermal barriers. Sensitization rate may be even greater in patients that have had lesions curetted. The seven days between the first two treatments for the patients enrolled in the Phase 3 studies may be insufficient to elicit contact sensitization. Additionally, adverse event data were not collected in a manner to differentiate phototoxic from allergic reactions. Additional safety assessment of retreatment with TRADENAME Cream is needed.

New data from a provocative study in normal human volunteers indicates that the contact sensitization rate is extraordinarily high at over 52% (Study PC T110/03). The Applicant contends (Vol. 1, pg. 108) that the clinical relevance of these findings is highly questionable since the study conditions differ markedly from actual clinical use. Under the proposed label conditions (e.g., lesion preparation) MAL Cream will be applied to abraded skin which might increase the potential for sensitization; however, sensitization potential under clinical use condition are unknown. Contact sensitization cannot be assessed based on the clinical trial dataset since safety data were not collected during the clinical trial in a manner to ferret adverse events due to sensitization. The seven days between the first two treatments for the patients enrolled in the Phase 3 studies may be insufficient to elicit contact sensitization. Safety and efficacy beyond the first two

treatment sessions have not been studied and are needed for adequate risk management assessment.

Contrary to the Applicant's assessment that no cross sensitization was demonstrated, cross-sensitization of MAL Cream with 5-aminolevulinate (an endogenous substance) results are inconclusive; however suggestive in that two equivocal results were obtained under conditions of the study (see Study PC T110/03). Additionally, the challenge phase of Study 110/03 was not adequately blinded; therefore, introduction of bias cannot be ruled out. Cross-sensitization with 5-aminolevulinate (ALA), an endogenous substance is of concern and cannot be ruled out based on Study PC T 110/03.

Clinical Pharmacology

(Note that Study PC T212/00 is being reviewed for safety).

Study PC T212/00

Title: "A Phase II, Randomized Study of Phototoxic Reactions in healthy Volunteers Following PhotoDynamic Therapy (PDT) with Metvix® 160 Mg/G Cream or with Cream Containing 20% 5-Aminolevulinic Acid (ALA)".

Study report location Volume 9 of 9, page 1

Study dates: (First subject treated October 2000 & last subject treated November 2000)

Objectives:

The primary objective was to compare the local phototoxic response following PDT with Metvix and PDT with ALA in healthy volunteers.

Secondary objects were to compare the two treatments with respect to:

- pain during and 24 hours after treatment (VAS – scale)
- change in fluorescence from before to 5 hours after cream application
- amount of substance P (a neuropeptide predominately occurring in primary sensory neurons known to be a primary sensory afferent neurotransmitter for mediating pain nociception) present immediately following illumination
- adverse events not related to local phototoxicity

Study Design

Blinded, prospective, randomized, within subject comparative study in healthy volunteers treated with Metvix-PDT or ALA-PDT/ — in Psoralen cream base.

Study Procedures

Site preparation consisting of lightly stripping the skin several times with adhesive tape, cream application under occlusion with Tegaderm and a light impermeable dressing for 5 hours, cream removal, followed by illumination with a 1200 Wyatt metal halogen lamp. A fluence rate of 180 mW/cm² and a total dose of 75 J/cm² were used. Each subject was followed for 4 weeks.

Pain was assessed during the procedure and 24 hours after on a 10-cm visual analog scale. Fluorescence was measured at baseline (before cream application) and immediately before illumination. Biopsies for determination of amounts of substance P by immunohistochemistry was taken immediately following illumination.

Adverse events including other phototoxic reactions

Local phototoxicity other than the symptoms included in the main parameter (erythema, edema, and hyperpigmentation) were also recorded on adverse events page in the CFR. safety was assessed. Pain, erythema, edema, and hyperpigmentation) were reported as AEs in the final report.

Study Population

Thirty-four (34) subjects were planned, randomized, and treated. There were 11 males and 23 females with age range of 19–47 (mean of 31). Subjects with known allergy to methyl-ALA, 5-aminolevulinate acid, a similar compound or excipients of the cream were excluded per protocol.

According to the Applicant, there were no amendments or protocol deviations reported; however, treatment was stopped for Subject 19 due to pain. Clarification from the Applicant has been requested for down grading the pain assessment from severe (as per comment) to moderate (Vol.9 of 9, pg. 200). Back pain (present prior to therapy) was listed. One case of severe edema and seven cases of moderate erythema were reported immediately after illumination with MAL-PDT.

Table 7: (Applicant's Table 36, Vol. 9 of 9, page 53. Description of adverse events. Local adverse events. Safety/ITT

WHO preferred term	Total		Relationship to treatment			
			Yes			
	Severity		Moderate		Mild	
			N	%	n	%
Pain skin	2	33	2	100	0	0
Itching	1	17	0	0	1	100
Erythema	1	17	1	100	0	0
Dermatitis Contact	1	17	0	0	1	100
Pruritus	1	17	1	100	0	0
Total	6	100	4	67	2	33

Reviewer comments:

According to the Applicant (Response to Question 1, pg. 3, Submission N-000 (BM), received October 31, 2003), adverse events can not be presented by treatment group because the AE form did not request any information about the location of the AE. However, it is noted that the CRFs submitted in response to other queries segregates AEs according to left side and right side (e.g., Methy-ALA vs. ALA).

Exanthema in follow-up is listed (Vol.9 of 9, pg. 200) for Subject 29 (in addition to phototoxicity (mild edema and moderate erythema); however, not included in the Listing 8: Listing of adverse events (pg. 202). According to the Applicant, exanthema was a typographical error and should have been erythema.

E. Summary of Critical Safety Findings and Limitation of Data**Unresolved Safety Issues**

The application is lacking adequate risk management for retreatment and additional treatments. The extent of drug exposure was not documented in Phase 3 studies. Adequate biochemical and hematological laboratory assessments have not been performed in actinic keratosis patients.

VIII. Dosing Regimen and Administration Issues

According to the proposed label, cream application should be 2.5 but no more than 4 hours prior to cream removal and illumination. However, clinical trials were performed using 2 lamps and data were not provided addressing total treatment times for multiple widely spaced lesions. Additionally, the proposed label recommends use of up to — of TRADENAME Cream per treatment session; however, reliable data are not available to support safe use of — Based on new PK data submitted by the Applicant, use of no more than 1g (half tube) should be applied per treatment session.

IX. Use in Special Populations (*Use in special populations review remain unchanged.*)**X. Conclusions and Recommendations****Conclusions****1) Potential For Skin Sensitization**

With other therapies readily available for treatment of AK, an approval for use as second line therapy is being made based on the extraordinarily high contact sensitization of over 52% in conjunction with lack of retreatment data, and long term safety.

Reviewer comment:

The Applicant contends (Vol. 1, pg. 108) that the clinical relevance of these findings of sensitization is highly questionable since the study conditions differ markedly from actual clinical use. Under the proposed label conditions (e.g., lesion preparation) MAL Cream will be applied to abraded skin which might increase the potential for sensitization; however, sensitization potential under clinical use condition are unknown. Contact sensitization cannot be assessed based on the clinical trial dataset since safety data were not collected during the clinical trial in a manner to ferret adverse events due to sensitization. The seven days between the first two treatments for the patients enrolled in the Phase 3 studies may be insufficient to elicit contact sensitization. Safety and efficacy beyond the first two treatment sessions have not been studied and are needed for adequate risk management assessment.

Contrary to the Applicant's assessment that no cross sensitization was demonstrated, cross-sensitization of MAL Cream with 5-aminovulinate (an endogenous substance) results are inconclusive; however suggestive in that two equivocal results were obtained under conditions of the study (see Study PC T110/03). Additionally, the challenge phase of Study 110/03 was not adequately blinded; therefore, introduction of bias cannot be ruled out. Cross-sensitization with 5-aminovulinate (ALA), an endogenous substance is of concern and cannot be ruled out based on Study PC T 110/03.

2) Instructions for Prevention of Sensitization of HealthCare Professionals Handling the Cream

Reviewer comment:

The Applicant provided text and diagrams for labeling addressing prevention of sensitization of healthcare professionals. Nitrile gloves should be worn when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection when using this product.

See Chemistry review for details.

- 1) Develop visual instructional material (e.g., video, CD, etc.), as part of labeling, to ensure the safe and effective use of the drug-device. The treatment process appears to be fairly complicated and such an aid should allow for safer (for both practitioner and patient) and more effective use of your drug/device.

Reviewer comment:

Illustrations depicted in the label are acceptable. The video is under review by DDMAC and CDRH.

Although considered a device issue, at the date of this review, data were not submitted to support the Universal Precautions method proposed by the Applicant for between patient use of the device (See CDRH Review

7

- 2) The Sponsor's Package Insert was modified in the enclosed draft labeling to provide information for the practitioner addressing safety concerns and information needed for use of this drug product. Of note was the need for laboratory data to support systemic safety profile; however, from the data submitted, a few clinically relevant treatment-emergent laboratory abnormalities have been reported and were not considered treatment related. As submitted, there does not appear to be a systemic safety signal for laboratory or non-local adverse event.

Reviewer comment:

Systemic biochemical and hematological laboratory parameters should be obtained in patients with AKs. The data obtained from patients with from previous studies may not be applicable to patients with AK due to differences in amount of drug exposure since AK lesions tend to be multiple. Data from the animal and clinical studies submitted indicate that there is little potential for hepatotoxicity with topical application of TRADENAME Cream, these data can be obtained in Phase 4 post-marketing study.

- 5) Submit the clinical trial results of Study PC T212/00 which is a Phase 2 randomized, comparative phototoxicity study of TRADENAME cream vs. ALA 20% cream applied for 5 hours conducted in healthy individuals. Submit a complete safety update including all safety data from other studies conducted with TRADENAME cream.

Reviewer comments:

No safety data with use of TREADENAME Cream could be garnered from this study due to the Applicant's method of data collection for this study (See Review).

- 6) Commit to conduct the following Phase 4 post-marketing studies:
 - A. A clinical 12-month study in at least 200 evaluable patients with 10 or more lesions (located on the face and scalp) in whom the following are collected: hepatic transaminases (ALT and AST), alkaline phosphatase, total bilirubin, and complete blood count plus differential data both at baseline and at one week after the second repeat dose 7-day regimen.
 - B. A longer-term clinical study documenting the effects of multiple retreatments and recurrence rate with this product. Actinic keratoses may be considered to be a chronic intermittent disease and multiple retreatments are common, especially in older, sun-overexposed patients.
 - C. A clinical dermal safety study to determine the photoallergenicity potential of TRADENAME Cream with a diluted form of TRADENAME Cream.
 - D. A safety and efficacy Phase 4 study of TRADENAME Cream in patients of Asian and in patients of Hispanic heritage.

Reviewer comments:

The Applicant proposed a modified post-approval clinical trial that did not include laboratory monitoring. Laboratory monitoring is recommended (See reviewer comments above).

The Applicant states that PhotoCure cannot agree for scientific reasons to a clinical dermal safety study of photoallergenicity potential of TRADENAME Cream. According to the submission, since UVA is an efficient activator of PpIX (Buchczyk et al 2001), it will be impossible to distinguish phototoxic reactions from photoallergenicity. Instead the Applicant proposes monitoring allergic skin reactions in the Phase 4 study as to type and distribution which may suggest causation. The Applicant's proposal to monitor allergic skin reactions (e.g., the type and distribution may suggest cause) in the large Phase 4 study is acceptable.

7) Package Insert

The Sponsor's Package Insert was modified. Reviewer comments regarding acceptability of the modifications are itemized and addressed in Appendix 1.

I. Recommendations

A. Recommendation on Approvability

An *Approval* recommendation is being made for NDA 21-415 for use of methyl-aminolevulinate-PDT in treatment of non-hyperkeratotic actinic keratosis (AK) of the face and scalp when used as supplementary to curettage in non-immunocompromised patients in the physician's office when other therapies are unacceptable or considered less appropriate. Approval as second line therapy is being recommended due to the high rate of sensitization of TRADENAME Cream and lack of retreatment and adequate long-term safety data. This application is for a drug-device combination and approval is contingent upon an approval recommendation from CDRH for the PhotoCure™ Halogen PDT Lamp (Model: CureLight 01).

B. Recommendation on Post-Marketing Studies and/or Risk Management Steps

In predisposed individuals, actinic keratosis is a chronic condition in which the number of lesions increases with advancing age; therefore, additional treatments are expected. Risk management provided by the Applicant is deficient regarding safety and efficacy of retreatment. Adequate long-term safety data were not provided. Adequate risk management with repeated use of TRADENAME Cream is needed for this drug product that exhibits such an extraordinarily high contact sensitization potential. Therefore, as a condition of approval, the Applicant should agree to conduct a 12-month safety study in at least 200 evaluable patients with 10 or more lesions, documenting the effects of retreatment of lesions with partial response after 3 months and treatment of new lesions. Laboratory monitoring should be performed.

Data from the animal and clinical studies indicates that there does not appear to be a potential for hepatotoxicity with topical application of TRADENAME Cream in BCC patients. It is uncertain whether laboratory parameters were obtained under maximal exposure conditions that would be comparable to post approval use in AK patients. There is no documentation of the amount of drug exposure in these studies; therefore, laboratory data are needed for AK patients with extensive disease. These data can be obtained in Phase 4.

C. Labeling Recommendations:

The Label is reviewed separately; however following labeling recommendations are of note:

- 1) Use of methyl-aminolevulinate-PDT as second line therapy (where other therapies are considered contraindicated) in treatment of non-hyperkeratotic actinic keratosis (AK) of the face and scalp when used as supplementary to curettage
- 2) Dispensing of medication should be to physicians only. According to the proposed label, this product is not intended for application by patients or unqualified medical personnel, therefore, this product should only be dispensed to and applied by physicians.
- 3) Healthcare professionals should wear nitrile gloves when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection when using this product.

Appendix

Additional Information needed for the Package Insert

Additional information needed as a condition of approval for the Package Insert and reviewer comments regarding adequacy of the Applicant's response are listed below.

A. Identify types of gloves which methyl-ALA and excipients found in TRADENAME Cream will not penetrate.

Reviewer comment:

Data supporting adequacy of the types of gloves that TRADENAME Cream will not penetrate is acceptable (See Chemistry review for details). Nitrile gloves should be worn when applying and removing the cream. Vinyl and latex gloves do not provide adequate protection when using this product.

B. Submit the line listings and serum transaminase level information for the patients treated with TRADENAME Cream in the BCC study(ies).

Line listings containing laboratory parameters ALAT, ASAT, and bilirubin from both BCC and AK patients were submitted.

Reviewer comment:

It is uncertain whether these laboratory parameters were obtained under exposure conditions that would be comparable to post approval use in AK patients (See response to C for further details).

C. Describe the lack of safety monitoring in Phase 3 studies to evaluate the potential for systemic adverse events for signals found in preclinical studies. Specifically, key concerns regarding potential for hepatotoxicity also should be addressed by changing the INDICATIONS AND USAGE section to provide for use of this product only in patients without evidence of liver disease, and the PRECAUTIONS section to have practitioners obtain serum transaminases (LFTs) before and after treatment with TRADENAME Cream in patients given TRADENAME Cream due to a lack of sufficient information in humans regarding hepatic enzyme elevations as were seen in animal studies with TRADENAME Cream.

New line listings and serum transaminase level information for the patients treated with TRADENAME Cream in the BCC studies and in the AK studies are submitted

The listings contain the laboratory parameters ALAT, ASAT and Bilirubin from the following studies:

PC T101/97 (16 patients with BCC)

PC T202/98 (119 patients with AK)

PC T203/98 (146 patients with BCC)

PC T204/98 (12 patients with AK)

PC T205/98 (94 patients with BCC)

Listing 1 shows individual patient data before and after PDT. The change from before to after PDT is presented as the difference between before and after values and as

percentage of reference range. The time in days between before and after PDT measurement is also presented.

Listing 2 shows the patients with clinically significant changes in laboratory parameters as judged by the investigator. Four patients were reported with clinically significant changes from the five studies. Patient 0075 in study PC T203/98 had an ALT value out of range for unknown reason, present before treatment. Patient 0103 in study PC T203/98 had ALT and AST values out of range before treatment, explained by concurrent diclofenac treatment. Patient 0274 in study PC T203/98 had an increase in bilirubin value from 10.7 to 23.8 micro mol/L for an unknown reason 8 days after PDT. Patient 0004 in study PC T204/98 had significant increased values of ALT and AST after PDT. However, these values were elevated before PDT, and the changes were not considered clinically significant.

Listing 3 shows the patients with an increase following PDT of more than 40% of the reference range. From the five studies 18 patients had an increase of more than 40% of the reference range in 23 laboratory values after PDT. Five increases were from above to above reference range, 11 were from within to within reference range and 7 were from within to above reference range.

Listing 4 shows the patients with a decrease following PDT of more than 40% of the reference range. From the five studies 17 patients showed a decrease of more than 40% of reference range in 20 laboratory values after PDT. Five decreases were from above to above reference range, 7 were from within to within reference range and 8 were from above to within reference range.

Applicant's Conclusion:

None of the clinically significant changes in laboratory parameters judged by the investigator were due to PDT with the TRADENAME cream. None of the increases were more than 2 times the upper reference range limit. Similar numbers of patients showed an increase as compared to a decrease of more than 40% of the reference range indicating no systematic changes after PDT.

Reviewer Comment:

In Study 202/98 and Study 205/98, patients received only a single treatment. Study drug concentration and application times varied in both studies. In Study 205/98, 78 patients with a different indication were treated with two treatment sessions per cycle. No treatment related laboratory abnormalities were noted in the studies as conducted. It is uncertain whether laboratory data from these patients can be extrapolated to AK patients since AK lesions can be numerous.

The amount of drug exposure has not been adequately documented in the Phase 2 and 3 studies. Due to differences in surface area of involvement, supporting biochemical and hematological laboratory parameters collected in patients with a different indication may not be applicable to patients with actinic keratoses. Overall, the patients studies have fewer lesions than those typically occurring in patients with AKs. Additionally, large lesions were excluded from most studies except for Studies 203/98 and 310/00.

Biochemical and hematological laboratory parameters were assessed in only 30 patients with actinic keratoses treated with the to-be-marketed concentration in Study 202/98. Additionally, these parameters were obtained after only one treatment whereas the labeled regimen is for two treatments.

Data from the animal and clinical studies indicates that there is little potential for hepatotoxicity with topical application of TRADENAME Cream in BCC patients. However there is no documentation of the amount of drug exposure in these studies nor in the Phase 3 studies; therefore, laboratory data are needed for AK patients with extensive disease. Laboratory biochemical and hematological parameters can be collected during conduct of the post-marketing safety study.

D. Provide the maximum duration of time permissible between application and illumination. Please provide information regarding needed adjustments to duration of light treatment following inadvertent prolonged exposure to TRADENAME Cream before light exposure. Provide information regarding what a patient should do if there is prolonged exposure without subsequent light treatment - e.g. avoidance of sunlight for how many days. All of these pieces of information should be supported with data. *Summary data were submitted from Studies 305 and 306 and the Applicant proposes 3-hour application time (at least 2.5 hours, but no more than 4 hours).*

Reviewer comment:

This response is acceptable.

E. Modify labeling so that patients are instructed to rinse off cream when left on for longer application periods than supported by data and to avoid illumination to the treated area(s). It is unknown whether the risk of illumination after longer application periods (e.g., up to — as previously asserted) with NDA 21-415 TRADENAME Cream is warranted for the treatment of actinic keratosis.

According to the Applicant, data from Study PC T206/98 in which TRADENAME Cream was applied to lesions for 28 hours indicates that the local AE profile are similar to other studies using 3 hours application times. Based on these data, the Applicant states that

Reviewer comment:

This response is acceptable.

F. Provide instructions for what should be done with light overexposure. This may be similar to management of burns from other causes.

According to the Applicant, during red light treatment there is a slight heating effect on the skin, but not to the extent that any harmful temperatures are reached. In the case of light overexposure resulting in burns, treatment should be the same as treatment for burns from other causes, and health personnel will be instructed to treat the burns according to AMA standard of practice guidelines for treatment of burns. We propose the following text to be inserted in the package insert in section OVERDOSAGE – Red Light Overdose:

“In that red light overexposure and skin burn occurs, the patient should be treated according to – standard of practice guidelines for treatment of burns.”

Reviewer comment:

This response is acceptable; however, the wording should be modified to comply with Patient package Inset Guidance (See PPI review).

G. Submit a Patient Package Insert to describe to patients the details and the safety aspects of the PDT procedure with TRADENAME Cream.

Reviewer comment:

The Patient package Insert has been reviewed by the Office of Drug Safety (ODS) and was deemed to be inadequate. Resubmission is pending at the time of this review.

H. Provide information regarding the radiant heat and temperature achieved with skin surfaces exposed to the Curelight Model 01 device. This information should also be provided to the CDRH device reviewer.

A study to provide information regarding the radiant heat and temperature achieved with skin surfaces exposed to the CureLight Model 01 device has been conducted. According to the Applicant, the results show that there is a slight heating effect on the skin, but not to the extent that any harmful temperatures are reached.

Reviewer comment:

Review by CDRH is pending.

I. Provide information and rationale regarding how long the redness and swelling should last before the patient should contact their doctor. This should be supported with data from studies.

According to data from the vehicle controlled studies, the median duration (in days) of mild, moderate and severe instances of erythema (redness) and skin edema (swelling) among all patients (N=149) treated with TRADENAME cream in the placebo-controlled phase III studies (PC T305/99 and PC T306/99) were presented. All events were resolved without medical treatment.

Moderate to severe instances of erythema which resolved without medical treatment had a median duration of 7 to 14 days with a maximum duration of 14 to 33 days. Since moderate to severe instances of erythema could last for up to 1 month, the patient should not contact their doctor until after 3 weeks.

Moderate to severe instances of skin edema which resolved without medical treatment had a median duration of 4 to 6 days with a maximum duration of 7 to 14 days. Since moderate to severe instances of skin edema could last up to 2 weeks, the patient should not contact their doctor until after 3 weeks.

PhotoCure proposes no changes in the Package Insert, which currently reads under PRECAUTIONS - General:

“Redness swelling is an expected result of therapy; however, if these symptoms increase in severity and persist longer than 3 weeks, the patient should contact their doctor.”

This information is also included in the draft Patient Package Insert.

Reviewer comment:

The response is acceptable.

J. Provide data regarding how long it takes for the surrounding skin reddening, swelling, crusting, blistering, edema, ulceration, peeling, itching and bleeding to resolve.

Data were submitted from the Phase 3 controlled studies regarding median duration of moderate and severe instances of burning sensation, erythema, edema, crusting, blistering, ulceration, peeling, itching and bleeding skin among all patients (N=149) treated with TRADENAME Cream

According to the data, The majority of events were resolved within 7 days after treatment with TRADENAME Cream, however moderate to severe local erythema could last for up to 14 days after treatment, on rare occasions up to 1 month.

PhotoCure proposes the following statement in the Patient Package Insert:

“These treatment; redness may be within 10 days of 1 month.”

Reviewer comment:

The response is acceptable; however, should be modified by deleting the word

K. Provide data regarding actual percentages of patients with peeling, bleeding, itching and severe pain in patients aged 65 and older (being greater than that in younger patients).

According to the Applicant, the safety results described in the Package Insert under the section “Geriatric use:” are based on data from 149 patients that were treated with the TRADENAME Cream in all placebo-controlled phase III studies of actinic keratosis.

These results deviate from the safety results from the 383 patients that were treated with the TRADENAME cream in all clinical studies of actinic keratosis (see section 11.1.2 in Integrated Summary of Safety). The safety results from all clinical studies with the TRADENAME Cream of actinic keratosis suggest that the profile of local and non-local adverse events in patients <65 years did not differ from that in patient >65 years (see section 11.1.3 in Integrated Summary of Safety).

We therefore propose the change in the Package Insert, under PRECAUTIONS – Geriatric use:

“Geriatric use: Seventy percent (269 of 383) of the patients treated with TRADENAME Cream in all clinical studies of actinic keratosis were 65 years of age or older”

Reviewer comment:

The response is acceptable; however, the wording will be changed to be consistent with

CFR wording (See Labeling review).

L. Provide the proportion of patients treated with TRADENAME Cream with adverse events. The denominator for adverse events should not be diluted with vehicle or other treatments.

According to the Applicant, 383 patients were treated with TRADENAME Cream in all studies of actinic keratosis (see table 44 in the Integrated Summary of Safety). 78% (297 patients of 383) of patients reported 1 or more adverse events. The majority of patients (74%: 282 /383) reported local adverse events, and 22% (83 / 383) reported non-local adverse events.

A total of 8 patients with AK and treated with TRADENAME Cream discontinued because of an adverse event. Three patients discontinued because of adverse events that were serious, that were dementia (patient 28 in study 202/98), pulmonary edema (patient 6 in study 204/98, who died due to heart failure) and kidney stone (patient 210 in study 301/99). None of these events were related to treatment. According to the database, one patient (patient 168 in study 202/99) was withdrawn from the study due to adverse events (erythema, skin ulceration and crusting). However, according to the CRF, the patient was withdrawn one month after the second treatment due to intercurrent disease (late stage Alzheimer's). The correct number of withdrawals /discontinuations due to local pain on illumination among the 383 patients is 4. Therefore, the Applicant propose to correct the number of withdrawals/discontinuations due to local pain on illumination in the Package Insert from 7 to 4 and to add the percentage of patients.

The following change was made in the Package Insert under ADVERSE REACTIONS – Adverse Experiences Reported by Body System:

“There were 4 (1.0%) withdrawals/discontinuations among 383 patients treated with TRADENAME Cream in the clinical trials of actinic keratosis, all of which were due to the adverse event of local pain on illumination.”

Reviewer comment:

This response is acceptable.

M. Provide the percentages and proportions for adverse events based on occurrence(s) per patient.

The Applicant provided the following set of tables showing the percentages and proportions for adverse events based on occurrence per patient.

Table 1 shows the number of local adverse events by severity and relationship to treatment for the studies PC T305/99 and PC T306/99. In total, 417 local adverse events among 130 patients were reported for the TRADENAME Cream and 50 among 61 patients for the placebo cream. For the TRADENAME Cream, 54% of the reported local adverse events were mild, 38% moderate and 8% severe. For the placebo cream, 88% were mild, 12% moderate and none severe. All (100%) of the local adverse events

reported for the TRADENAME Cream were related to treatment, compared to 94% for the placebo cream.

Table 2 shows the number of non-local adverse events by severity and relationship to treatment for the studies PC T305/99 and PC T306/99. In total, 71 non-local adverse events among 130 patients were reported for the TRADENAME Cream and 26 among 61 patients for the placebo cream. For the TRADENAME Cream, 55% of the reported non-local adverse events were mild, 39% moderate and 6% severe. For the placebo cream, 77% were mild, 23% moderate and none severe. 56% of the non-local adverse events reported for the TRADENAME Cream were related to treatment, compared to 15% for the placebo cream.

Table 3 shows the number of local adverse events per patient for the studies PC T305/99 and PC T306/99. In total, 107 of 130 (82%) patients that were treated with the TRADENAME Cream reported at least one local adverse event, compared to 25 of 61 (41%) patients treated with the placebo cream. Among the patients that reported local adverse events, the mean number of local adverse events was 3.9 for the TRADENAME cream and 2.0 for the placebo cream.

Table 4 shows the number of non-local adverse events per patient for the studies PC T305/99 and PC T306/99. In total, 39 of 130 (30%) patients that were treated with the TRADENAME Cream reported at least one non-local adverse event compared to 15 of 61 (25%) patients treated with the placebo cream. Among the patients that reported non-local adverse events, the mean number of non-local adverse events was 1.8 for the TRADENAME Cream and 1.7 for the placebo cream.

Table 5 shows the most frequent combinations of two local adverse events for the studies PC T305/99 and PC T306/99. In total, 40 of 130 (31%) patients that were treated with TRADENAME Cream reported burning sensation of the skin in combination with erythema. Erythema in combination with either skin pain or crusting or stinging or oedema were reported in approximately 15% of the patients. All other combinations of two local adverse events were reported in less than 10% of the patients.

The FDA proposed table in the Package Insert under ADVERSE REACTIONS: "Summary of local adverse events in subjects receiving 2 treatments" has been corrected based on data from the above mentioned tables, and is included in the new draft Package Insert:

Percentages for adverse reactions based on occurrence(s) per patient with 95% confidence intervals were provided.

The Applicant submitted other adverse reactions tabulations; however, the following table is most relevant and is included in the label. The Applicant submitted the following table in response to the request to calculate percentages for adverse reactions based on occurrence(s) per patients.

Applicant's Table 14

Percentage patients with local adverse reactions based on occurrence per patient in vehicle controlled phase 3 studies.		
Events	TRADENAME PDT Vehicle PDT* (n=130)	(n=61)
	% of patients with AEs	% of patients with AEs
Burning sensation skin	50.0%	14.8%
Erythema	46.2% 19.7%	
Pain skin	20.8%	9.8%
Stinging skin	19.2%	3.3%
Crusting	15.4%	9.8%
Oedema skin	15.4%	1.6%
Skin peeling	10.8%	3.3%
Blisters	10.8% 3.3%	
Bleeding skin	8.5%	3.3%
Pruritus	6.2% 3.3%	
Itching	6.9% 0%	
Skin ulceration	5.4%	0%
Skin infection	2.3%	1.6%
Rosacea	0% 0%	
Skin hyper-pigmentation	0.8%	0%
Skin disorder	0%	1.6%
Hyperkeratosis	0% 1.6%	

Reviewer comment:

Modifications to data presentation for the adverse events table have been made (See labeling review).

N. Provide information regarding severity of burning sensation and skin pain seen in U.S. and Australian studies.

The Applicant's response is that severe instances of burning sensation were reported by 10 out of 114 patients (9%) and severe skin pain was reported by 8 out of 114 patients (7%) in the U.S. (PC T306/99) and Australian (PC T305/99) studies.

The Applicant proposes the following changes will be made in the Package Insert, under ADVERSE REACTIONS -

Reviewer comment:

This response is acceptable; however, wording has been modified as follows:

O. Identify the light transmittance through 1 millimeter of TRADENAME Cream at 30°C.

According to the submission, the light transmittance through 1 mm of TRADENAME Cream at 30°C has been measured. The Applicant does not propose this information to be included in the Package Insert. A quartz cuvette with a 1 mm light path was filled with TRADENAME Cream and heated to 30°C. Light from a halogen lamp transmitted through the cuvette and into the aperture of an integrating sphere was measured with a fiber optical spectrometer. The transmittance was calculated by comparing to a measurement using the same setup with an identical cuvette filled with distilled water. The transmittance varied with the wavelength of the light and was lowest (16% transmittance) at 380 nm. The transmittance then increased with increasing wavelength and was highest (50% transmittance) at 700 nm.

Reviewer comment:

The response is acceptable.

P. Provide a list of anesthetics and the frequency with which they were used in Phase 3 studies.

The Applicant provided a list of anesthetics and the frequency with which they were used in Phase 3 studies. Patients who received anesthetics in the placebo controlled phase III studies PC T302/99, PC T305/99 and PC T306/99 were listed. The anesthetics used were xylocaine, xylocaine with epinephrine, lidocaine and lidocaine with epinephrine.

Nine patients out of 149 (6%) treated with the TRADENAME Cream received anesthetics, and for 7 of these it was reported that they received anesthetics for PDT. One patient received anesthetics because of excision of a BCC lesion and one because of excision of Bowen's lesion and biopsy of a hyperkeratotic lesion.

In the vehicle cream group, 4 patients of 80 (5%) received anesthetics and for 2 of these it was reported that they received anesthetics for PDT. Two patients received anesthetic because of biopsy of SCC.

PhotoCure proposes to delete the information regarding _____ from the draft Package Insert, and proposes to modify the text under CLINICAL PHARMACOLOGY – Clinical studies as follows:

The Sponsor proposes to delete the information ' _____ ' from the draft Package Insert under PRECAUTIONS – Information to Patients, and do not add this information in the draft Patient Package Insert.

PhotoCure also proposes to delete the following information from the draft Package Insert under DOSAGE AND ADMINISTRATION – _____

Reviewer comment:

_____ needs further study prior to making labeling recommendations.

Q. Identify the type of spatula used in clinical studies (e.g. what is the composition?).

In study PC T306/99, none of the centers have recorded the use of a spatula. The centers mainly applied the cream directly from the tube onto the prepared lesion, and used the transparent tape to spread it. One tube of cream was used per patient per visit. In study PC T305/99, the investigators used disposable, non-sterile, wooden tongue depressors as spatulas to apply the cream. Several different brands were used; e.g. —

Reviewer comment:

The response is noted.

R. Provide subgroup analysis with regard to wait time or information regarding compensatory calculations for lamp exposure during CureLight 01 light treatment.

In total, 620 lesions were treated with the TRADENAME Cream. No lesions was treated with application time below 2.5 hours. Application time was between 2.5 and 3 hours for 22 % (134 out of 620) , 66% (410 out of 620) between 3 and 3.5 hours, 11% (69 out of 620) between 3.5 and 4 hours, and 1% (7 out of 620) above 4 hours.

The lesion complete response rate was 84% for lesions treated with application time between 2.5 and 3 hours, 90% for lesions with application time between 3 and 3.5 hours and 78% for lesions with application time between 3.5 and 4 hours. The lesion response rate was similar in the three application categories covering application times between 2.5 and 4 hours.

This corresponds with the time frame of 2.5 to 4 hours as proposed in the package insert.

Reviewer comment:

The response is acceptable.

S. Provide explicit procedures for use of the device (CureLight 01 lamp) that would allow for adequate patient protection and prevent cross-contamination (i.e., Universal Precautions), yet at the same time, not hinder effective use.

Use of the sleeves

According to the Applicant, protective disposable sleeves have been developed for the horseshoe-positioning device and for the light-measuring probe, as these are the only parts of the lamp that get in contact with the patient's skin.

The use of the sleeves is described in the User Manual, version 2.4 (enclosed in Attachment 12) under Operating Instructions on the following pages:

Page 12: "To avoid direct contact between lamp parts and the patient skin, always use the disposable protective plastic sleeve on the positioning device and on the light measuring probe."

Page 13: "Snap on the disposable protective plastic sleeve on the underside of the horseshoe shaped positioning device."

Page 14: "Snap on the disposable protective plastic sleeve on the underside of the light measuring probe."

Page 15: "Remove the protective plastic sleeve from the positioning device and from the light measuring probe. Discard the plastic sleeves."

The disposable protective sleeve for the light-measuring probe is used during calibration of the light source. The light-measuring probe is placed in the center of the light field on the skin lesion. This calibration operation takes normally approx. 10 seconds. As can be seen from the pictures in the User Manual (page 14), the disposable sleeve on the probe does not cover the topside where the light sensor is situated. Hence the light measuring and therefore the calibration are not affected in any way.

The disposable protective sleeve on the horseshoe-positioning device is used during calibration and light treatment. The horseshoe-positioning device is placed on normal skin near the lesion surface and it assists in positioning of the lamp and the adjustment of the light field. The procedures normally take less than 10 minutes. One patient is exposed to 1- 4 treatments. The disposable protective sleeve does not hinder effective use of the horseshoe-positioning device.

A _____ has been selected as a suitable material for the protective sleeves. The selection was based on the _____ is used as a guide for selection of material and testing of the plastic sleeves.

Information from the literature, communication with medical device manufacturers and suppliers of plastic material, resulted in the _____ as suitable material for the disposable, protective sleeves.

Since the Sponsor proposes to use disposable plastic sleeves, the Sponsor proposes to delete the following text in the Package Insert under WARNINGS proposed by the Division:

*Further more, the Division proposed to include the following statement under PRECAUTIONS – Information for Patients:
Final Date: 30 June 2003 38PhotoCure ASA Clinical Data Methyl aminolevulinate Cream 168 mg/g Response to Approvable Letter NDA 21-415 Amendment July 2003*

The sponsor is of the opinion that this warning does not need to be included in this section, as it is the health practitioner alone who will be responsible for following the instructions for disinfecting the lamp as specified in the lamp User Manual. In addition, the introduction of disposable plastic sleeves that will be changed between each patient, cancel risk of contamination. We therefore propose to delete this statement from the section Information for patients.

The sponsor proposes the following adjusted text in the Package Insert under DOSAGE AND ADMINISTRATION, Step 5 of the procedure (Illumination of TRADENAME Treated Lesion):

“The CureLight BroadBand Model CureLight 01 lamp is approved for the use in TRADENAME-PDT. The lamp should be carefully calibrated so that dosing is accurate and immediately thereafter the lesion should be exposed to red light with a continuous spectrum of 570 to 670 nm and a total light dose of 75 J/cm². To avoid direct contact between lamp parts and patient skin, always use disposable protective plastic sleeves on the positioning device and on the light measuring probe. Following each treatment, the disposable protective plastic sleeves should be removed from the positioning device and from the light measuring probe and discarded.”

This text describes the specific characteristics and use of the approved Curelight BroadBand Model Curelight 01. Elsewhere in the package insert the use of more generic terms such as “red light illumination” and “approved lamp” are proposed, except when referring to specific studies performed.

Model Curelight 01.

Reviewer comment:

Adequacy of the proposed modification to the device to provide adequate patient protection is under review by CDRH.

T. Provide information/description for treatment of multiple actinic keratosis lesions in one treatment session (e.g., multiple lamps vs. single lamp, staggering of lesions).

For treatment of multiple AK lesions in one treatment session, it is only possible to use multiple lamps simultaneously if the lesions are relatively widely separated. The design of the lamps is such that it is physically not possible to place two lamps side by side in such a way as to get two overlapping light fields.

In the clinical studies, patients with multiple, separated lesions were treated simultaneously with two lamps. The reason was to keep the treatment time within reasonable limits.

Multiple AK lesions may also be treated in a staggered (sequential) fashion. In this case it is noted that should overlapping areas be illuminated sequentially, re-illumination of parts of an already illuminated field (the overlap area) would not have any effect (as there would be no photoactive porphyrins present in the overlap area due to PpIX depletion during illumination).

Thus, multiple lesions may be treated simultaneously using more than one lamp if the lesions are relatively widely separated, or treatment of multiple lesions may be staggered.

Thus, we propose the following slightly modified text in the Package insert section DOSAGE AND ADMINISTRATION:

*We further propose to modify the following statement –in the Patient Package Insert:
“Multiple lesions may be treated during the same treatment session*

Reviewer comment:

Safety data regarding overlapping fields or treatment of clustered lesions was not addressed during the clinical trials and it is unknown whether burns and ulceration of the treated lesions might occur. Treatment of multiple actinic keratosis lesions in one treatment session (e.g., multiple lamps vs. single lamp, staggering of lesions) has not been adequately addressed by the Applicant; however, can be obtained in Phase 4.

U. Provide information regarding effect of local anesthesia and increased pain intolerance on adverse events (i.e., were patients who were given local anesthesia more likely to have burns due to failure to feel discomfort and/or were they less likely to report local adverse events such as pain and stinging?).

A total of only 7 of 149 patients (5%) that were treated with the TRADENAME cream and 2 of 80 patients (3%) that were treated with the placebo cream received local anesthetics for PDT. Three out of 7 patients (43%) that were treated with the TRADENAME cream reported burning. Taking into consideration the low number of patients that received local anesthetic for PDT compared to the overall safety database for the placebo controlled phase III studies, where 49% of the patients treated with the TRADENAME cream reported burning sensation, there is no indication that patients who were given local anesthesia were more likely to have burns due to failure to feel discomfort.

The evaluation of whether the patients that received local anesthetics were less likely to report local adverse events such as pain is difficult since the patients were given local anesthetics because they reported pain. None of the studies routinely administered local anesthetics before the start of PDT.

Reviewer comment:

The number of patients receiving local anesthetics is too small to make an accurate assessment. The effect of local anesthetics on safety and efficacy needs to be systematically studied and can be assessed in Phase 4.

V. Provide information regarding what should be done with the lesion area after exposure to red light treatment with the CureLight 01 lamp.

In the clinical studies, each investigator instructed the patients to treat any reactions, such as swelling, burning, crusting, etc., occurring after light treatment according to office/clinic practice guidelines. PhotoCure does not propose to include any new information in the Package Insert.

PhotoCure proposes to reword the following text proposed by the Division as Information to the Patient, now moved to in the Patient Package Insert:

PhotoCure proposes to continue this section by including the following sentence:

Reviewer comment:

The Patient Package Insert is being rewritten and the patient instructions will be revised.

W. Submit a visual aid that will be part of labeling. The treatment process appears to be fairly complicated and such an aid should allow for safer (for both practitioner and patient) and more effective use of your drug/device.

PhotoCure has provided drawings as simple visual aid to be inserted into the labeling. PhotoCure proposes to include these drawings in the Package Insert in section DOSAGE AND ADMINISTRATION and the Patient Product Information.

Reviewer comments:

The visual aid is acceptable; however, the text has been modified (See Labeling Review).

X. Provide information on both light and drug overdose that are supported by data.

TRADENAME Cream overdose

We refer to question 4 D of this response.

CureLight 01 Overdose

Database for the two pivotal studies, PC T305/99 and PC T306/99 provides data on patients that received light intensities above 200 mW/cm². Twenty patients received an intensity above 200 mW/cm² during illumination in study PC T305/99. In the overall safety profile of study PC T305/99 and PC T306/99 (total population), 4% of the burning sensation reactions and 3 % of skin pain reactions were reported to be severe. There were more subjects in the total population that experienced moderate erythema, burning sensation and pain skin than the population that received light intensities above 200 mW/cm². It appears that the safety profile on the patients that received a light intensity larger than 200 mW/cm² did not differ from the total population.

Based on these data, the Applicant suggests the following rewording of the text in the package Insert OVERDOSE – Red Light Overdose:

“There is no information on overdose of red light following TRADENAME Cream application. .

Reviewer comment:

These numbers are too small to make an accurate assessment regarding safety profile on patients exposed to intensities up to 250 mW/cm². CDRH input on this issue will be addressed in the label.

Y. Identify if "_____ is appropriate to be placed _____
_____". (See Chemistry review for details.)

A _____ of TRADENAME Cream is described in NDA 21-415. In this study, cream samples were _____ to provide evidence of any alteration in physical composition. The results given in NDA 21-415 Vol. 7, Item 4B.9.9 indicate that the product is not adversely affected. _____ It is therefore not appropriate to list _____

Reviewer comment:

The response is acceptable (See Chemistry Review).

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

/s/

Brenda Vaughan
1/14/04 04:46:04 PM
MEDICAL OFFICER

Markham Luke
1/14/04 04:57:24 PM
MEDICAL OFFICER
Concur with approval or approvable pending resolution of device
issues and labeling.

Stanka Kukich
1/15/04 09:13:54 AM
MEDICAL OFFICER
signing for Dr. Jonathan Wilkin, Division Director

In
DFS
9/17/02
MEL

**Clinical Team Leader Addendum Memorandum for TRADEMARK
(methyl aminolevulinate) Cream 16.8% --- NDA 21-415**

September 17, 2002

This Memo highlights in brief the key changes to the submitted Package Insert for NDA 21-415. It is recommended that the Package Insert as modified be sent in the Action letter if an Approvable action is taken.

The major concerns with the submitted label that are addressed in the Agency's proposed labeling are as follows:

- 1) Information regarding the specific population that would benefit from the use of the Cream (INDICATIONS AND USAGE section). Key concerns regarding hepatotoxicity, which emerged during the NDA review process from pre-clinical studies submitted to the NDA, were addressed. Thus, the first paragraph of the INDICATIONS AND USAGE section reads as follows: "TRADEMARK cream in combination with 570 to 670 nm wavelength red light illumination using the CureLight BroadBand Model CureLight 01 lamp is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp in

The hepatotoxicity concern should have been addressed in the Phase 3 studies, however this was not possible due to the Sponsor's condensed development program where prerequisite pre-clinical pharm/tox studies were submitted at the same time as their Phase 3 studies. Ideally, the pharm/tox studies should have informed for the Phase 3 studies and hepatic monitoring should have been instituted during the human studies.

- 2) Information regarding the use of this product was not sufficiently detailed in the Sponsor's proposed labeling. This was addressed in the Agency's proposed label in the DOSAGE AND ADMINISTRATION section.
- 3) The Sponsor's proposed labeling did not address safety concerns for the Practitioner due to inherent contact hypersensitivity (as evidenced in the dermal safety studies), nor did it address concerns regarding Universal Precautions for blood-borne disease that may be transmissible via contact with contaminated instrumentation used in this procedure.

Additional information is requested from the Sponsor throughout the Package Insert for this product (Notes to Sponsor). Changes to other sections of the Sponsor's submitted Package Insert were also included. The Sponsor is also advised to provide a Patient Package Insert to facilitate safe and effective use of this product and inform the patient.

Clinical Team Leader, Dermatology,
Markham C. Luke, M.D., Ph.D.

Cc: HFD-540/ Vaughan, Wilkin, Nostrandt, Jacobs, Lutwak

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

/s/

Markham Luke
9/17/02 10:41:54 AM
MEDICAL OFFICER
Addendum Memo for methyl ALA

Jonathan Wilkin
9/17/02 02:16:14 PM
MEDICAL OFFICER
The MO and TL have also added to the
Precautions section of labeling that transaminases should be
obtained before and after treatment

**Clinical Team Leader Summary Memorandum for TRADEMARK
(methyl aminolevulinate) Cream 16.8%
NDA 21-415**

Revisions: July 21, 2002
August 16, 2002
September 12, 2002

Methyl aminolevulinate (methyl ALA) cream, 16.8% (TRADEMARK Cream, 16.8%) is a topically applied drug to be used for photodynamic therapy (PDT) for the treatment of actinic keratoses. This product does not yet have a trademark. The Applicant proposed trademark, Metvix, was found to be unacceptable by the Office of Drug Safety due to concerns that it may be confused with Mentax, another dermatological drug product that is also a cream. The product was classified as a 2S due to the fact that methyl aminolevulinate is a methyl ester of aminolevulinic acid (ALA). ALA is currently marketed as a topical solution (Levulan Kerastick) also for the treatment of actinic keratoses.

Actinic keratoses are common epithelial lesions found most often in fair-complected individuals. Actinic keratoses, while not considered to be malignant of themselves, occur in patients at risk for development of skin neoplasms. Whether actinic keratoses actually evolve into such skin neoplasms has not been definitively shown. Nonetheless, it is chronic sun exposure in fair-skinned persons that may lead to the occurrence of actinic keratoses so actinic keratosis is a fairly common disease.

Multiple concerns arose during the review process of this New Drug Application. These are noted by the primary Clinical, Pharmacology/Toxicology, and Biopharmaceutics reviews. Key concerns described were as follows:

The Pharmacology/Toxicology reviewer had information not submitted by the Applicant until the NDA submission that were relevant to informational needs for Phase 3 studies:

A) Systemic evaluation in rodents revealed effects primarily on red blood cell parameters and the liver. Clinical pathology findings suggestive of similar effects were seen in repeated dose topical studies in rats and minipigs. The following was recommended for labeling in the _____ section:

B) The drug substance was negative in dermal irritation screening, but was a positive sensitizer in guinea pig skin. There may be potential for sensitization in clinical patients.

C) In the rat study, serum ALA was seen to increase after the final dose. Additionally, an *in vivo*, radiolabeled pharmacokinetics study in the rat demonstrated 13.1% absorption of the drug substance across abraded skin. An *in vitro* study in rat skin vastly underestimated the degree of absorption *in vivo*. It is possible that absorption across curretted human skin may be greater than the sponsor theorizes.

D) Toxicokinetic evaluation was not performed in the minipig study, nor was microscopic examination of target tissues.

The following is recommended to be conveyed in the action letter:

Tissues collected in the repeated dose dermal toxicology study in minipigs should be evaluated histologically. At a minimum, the kidneys, liver, spleen, thyroid and bone marrow should be evaluated.”

The Biopharmaceutics reviewer had the following recommendations:

“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 [of drug and/or light (*sic*)] 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.”

The primary Medical Officer’s Review is thorough, deliberate, and describes the issues regarding the submission by the Applicant. Efficacy was clearly shown despite the relatively small numbers of patients evaluable in the two pivotal Phase 3 studies (111 patients in the Australian study with 88 on active and 80 in the U.S. study with 42 on active). However, the safety determination was complicated by a lack of laboratory monitoring in Phase 3 studies. The Applicant chose to proceed with Phase 3 development despite not having pre-clinical studies completed. Some of the pre-clinical information was submitted for the first time with the NDA and review of that data

suggest that further assessment of the serum transaminase levels is needed and would have been requested in Phase 3 studies had that information been submitted prior to the end of Phase 2.

Human serum transaminase levels were submitted for about 30 subjects for a single treatment study (larger pivotal studies had two doses of drug given, 7 days apart). These serum transaminase levels were normal. Studies conducted for a different indication with methyl-ALA, specifically, for treatment of basal cell carcinoma, were not submitted to this NDA. However, the Agency is aware of these studies

Some of those studies may also contain data relevant to evaluation of the effect of this drug on serum transaminase levels. The Medical Officer has asked that the Sponsor submit the line listings containing the needed data in any response to an Approvable action.

A perspective to consider with regard to systemic safety considerations for this drug is the fact that ALA is endogenously present as a precursor molecule in heme biosynthesis. Normal urinary excretion of ALA should not be more than 6.4 mg/24 hours. Normal random urinary ALA levels are as follows (Johns Hopkins Hospital, Department of Pathology Reference standards):

<u>Age</u>	<u>Urinary ALA</u>
1-8 years	2.3 – 6.2 mg/g
9-17 years	1.5 – 5.3 mg/g
>17 years	0.0 – 3.6 mg/g

Thus, the amount of methyl-ALA present in a 2 gram tube of TRADEMARK Cream (which is metabolically converted to ALA) appears to be acceptable for local topical application when compared to the amount of endogenous ALA present and excreted in normal humans, assuming that methyl-ALA does not have toxicities beyond those for ALA.

There are inherited and acquired diseases with elevations of ALA and other porphyrins (porphyrias). Elevated ALA in urine and serum is found in Acute Intermittent Porphyria (AIP) both during and between porphyria “attacks”. Elevated ALA in urine and serum is found in Variegate Porphyria, Hereditary Coproporphyrinuria and ALA Dehydratase Deficiency Porphyria (a very rare type of acute hepatic porphyria) during porphyria “attacks”. In AIP, urinary excretion of ALA can be as high as 100 mg/24 hours during an acute attack.

Transient elevations of ALA are seen in certain porphyrias, but the levels of ALA that are associated with symptoms of porphyria are much larger than that likely to be achievable from metabolism of methyl-ALA in TRADEMARK Cream (assuming the unlikely complete absorption of a 2 gram tube containing 33.6 mg of methyl ALA and complete conversion from methyl-ALA to ALA).

Pharmacokinetic studies were conducted and submitted to NDA. These were described in the Biopharmaceutics review. These studies are advised to be done under maximal use conditions. The maximum dose applied to subjects in the pharmacokinetic studies was 1 gram. Thus, systemic exposure for this drug was only formally assessed at 1 gram. More cream may have been used in Clinical studies, but it is not clear from the data submitted as to the amounts used and the relative safety profile associated with larger amounts of TRADEMARK Cream used.

It should be advised in labeling that no more than 1 gram of TRADEMARK Cream should be used at any one treatment session. This adjustment was made to the draft labeling.

The Sponsor has not adequately addressed the high rate of allergenicity and hypersensitivity seen in the provocative testing with methyl-ALA. Additionally, cross-sensitivity issues have not been adequately addressed with topical applications of methyl-ALA and ALA. No testing was conducted regarding this issue. Physicians and healthcare providers giving Metvix should be cautioned to wear gloves and not directly contact the Methyl-ALA. The Sponsor's complete response should address this allergenicity concern for patients and whether wearing gloves is sufficient to prevent allergenicity in providers. The MO has recommended a 21 day contact sensitization potential study looking at both ALA and methyl-ALA in the challenge phase prior to approval. Also needed are data driven instructions for prevention of sensitization of healthcare professionals. TL agrees that this is the best approach to getting this needed information for labeling.

The MO has recommended that an instructional video be made for distribution with the drug. The steps for application of this product and its use with the device are relatively complicated. It is suggested from the review and the information provided by the Sponsor that sufficient detail needs to be given to providers using this drug in order to have adequate safety with use of this product. The Dermatology TL is in agreement that such a video be included as a part of labeling.

Additional information is needed with regard to the results of Study PCT212/00, a comparative phototoxicity study comparing methyl-ALA cream vs. an ALA cream applied for 5 hours in healthy individuals.

Thus, the Clinical Team is in agreement that this product is Approvable. There are outstanding informational needs in order to label the product adequately for safe and effective use. The Applicant should address these prior to Approval. See also primary Clinical Review and Draft Labeling for additional information to be requested from the Sponsor (Informational needs for the Sponsor are Bolded in Draft Labeling). Phase 4 commitments are requested of the Sponsor to conduct additional studies to address informational needs for this product (see primary Clinical Review).

Clinical Team Leader, Dermatology,
Markham C. Luke, M.D., Ph.D.

Cc:
HFD-540/ Vaughan, Wilkin, Nostrandt, Jacobs, Lutwak

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

/s/

Markham Luke
9/13/02 08:48:59 AM
MEDICAL OFFICER
TL Summary Memo for TRADEMARK (methyl-ALA) Cream 16.8%

Jonathan Wilkin
9/13/02 12:39:25 PM
MEDICAL OFFICER

Clinical Review of NDA 21-415

APPLICATION NUMBER: 21-415

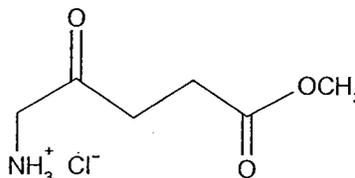
SUBMISSION/REVIEW DATES:
 CDER STAMP DATE: 09/26/01
 FILING DATE: 11/25/01
 REVIEW COMPLETED: 07/18/02

APPLICANT NAME: Photocure ASA
 ADDRESS: Hoffsveien 48
 N-0377, Oslo
 Norway

NAME OF COMPANY OFFICIAL
 OR CONTACT PERSON: Dr. William A. Clementi, Pharm.D., F.C.P.
 Clementi & Associates
 919 Conestoga Road
 Rosemont, PA 19010
 610-581-7021; (Fax: 610-581-7025)

NOMENCLATURE

TRADENAME: Tradename ® Cream
 GENERIC NAME: Methyl aminolevulinate hydrochloride
 CHEMICAL NAME: Methyl aminolevulinate hydrochloride
 CHEMICAL STRUCTURE:



MOLECULAR FORMULARS: $C_6H_{11}NO_3 \cdot HCl$
 MOLECULAR WEIGHT: 181.62
 DOSAGE FORM: Cream
 ROUTE OF ADMINISTRATION: Topical

REVIEWER: NAME: Brenda Vaughan
 TITLE: Medical Officer
 DIVISION: Dermatologic and Dental Drug Product

DOCUMENTS REVIEWED: NDA 21-415 volumes

NDA 21-415 BC	received	11-16-01
NDA 21-415 NC	received	12-14-01
NDA 21-415 BS	received	12-26-01
NDA 21-415 N-000 (SU)	received	01-25-02
NDA 21-415 BZ	received	02-27-02
NDA 21-415 BB	received	03-01-02
NDA 21-415 BC	received	04-08-02
NDA 21-415 NC	received	04-09-02
NDA 21-415 NC	received	04-10-02
NDA 21-415 NC	received	04-17-02

NDA 21-415 NC	received	04-19-02
NDA 21-415 BM	received	04-19-02
NDA 21-415 BB	received	04-22-02
NDA 21-415 BM	received	04-29-02
NDA 21-415 BB	received	05-06-02
NDA 21-415 BS	received	05-07-02
NDA 21-415 BC	received	05-29-02
NDA 21-415 NC	received	06-28-02
NDA 21-415 NC	received	07-05-02

Table of Contents

Table of Contents.....3

Executive Summary 5

I. Recommendations

A. Recommendation on Approvability5

B. Recommendation on Phase 4 Studies and/or Risk Management Steps.....5

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program.....8

B. Efficacy.....9

C. Safety10

D. Dosing.....17

E. Special Populations17

Clinical Review

I. Introduction and Background 19

**A. Drug Established and Proposed Trade Name, Drug Class, Sponsor’s
 Proposed Indication(s), Dose, Regimens, Age Groups19**

B. State of Armamentarium for Indication(s).....19

C. Important Milestones in Product Development.....19

D. Other Relevant Information20

E. Important Issues with Pharmacologically Related Agents.....22

**II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and
Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other
Consultant Reviews..... 22**

III. Human Pharmacokinetics and Pharmacodynamics..... 24

A. Pharmacokinetics.....24

B. Pharmacodynamics24

IV. Description of Clinical Data and Sources

A. Overall Data.....25

B. Tables Listing the Clinical Trials.....25

C. Postmarketing Experience26

D. Literature Review26

V. Clinical Review Methods

A. How the Review was Conducted.....26

B. Overview of Materials Consulted in Review26

C. Overview of Methods Used to Evaluate Data Quality and Integrity27

D. Were Trials Conducted in Accordance with Accepted Ethical Standards27

E. Evaluation of Financial Disclosure27

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions.....27

B. General Approach to Review of the Efficacy of the Drug28

C. Detailed Review of Trials by Indication.....28

D. Efficacy Conclusions54

VII.	Integrated Review of Safety	
	A. Brief Statement of Conclusions	55
	B. Description of Patient Exposure	56
	C. Methods and Specific Findings of Safety Review	59
	D. Adequacy of Safety Testing	68
	E. Summary of Critical Safety Findings and Limitations of Data	74
VIII.	Dosing, Regimen, and Administration Issues	77
IX.	Use in Special Populations	77
	A. Evaluation of Sponsor’s Gender Effects Analyses and Adequacy of Investigation	77
	B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy	77
	C. Evaluation of Pediatric Program	78
	D. Comments on Data Available or Needed in Other Populations	78
X.	Conclusions and Recommendations	
	A. Conclusions	79
	B. Recommendations	79
	C. Labeling Recommendations	82

CLINICAL REVIEW of NDA 21-415

Executive Summary Section

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Tradename Cream contains methyl aminolevulinic acid hydrochloride (methyl ALA), which is a methyl ester of aminolevulinic acid. The metabolism of aminolevulinic acid (ALA) is the first step in the biochemical pathway resulting in heme synthesis. Aminolevulinic acid and methyl ALA are not photosensitizers, but rather a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. Tradename Cream, plus illumination with the Curelight Lamp (a red light of 570 to 670 nm wavelength, is the basis for Tradename photodynamic therapy (PDT). This drug-device combination when used in combination constitutes Photodynamic Therapy (PDT) and is intended for treatment of actinic keratosis. Treatment is administered in a two-step process involving lesion preparation/drug application followed 3 hours later by illumination. The entire process is repeated in 7 days.

Efficacy has been demonstrated in two clinical trials with use of two treatment sessions of Tradename Cream-PDT over vehicle cream-PDT in treatment of actinic keratosis of the face and scalp when used as supplementary to curettage. From a clinical perspective, the application is *Approvable*; however, there are multiple concerns that are either unresolved or were not adequately addressed by the Sponsor in the submitted dataset.

The quality and quantity of the safety database submitted with the NDA application does not include enough information to exclude possible safety issues for the proposed dosing regimen. New data submitted for the first time at NDA submission and new information resulting from queries made by the Division during NDA review has made it evident that additional safety data is needed prior to approval while other informational needs can be derived from Phase 4 studies.

It is determined that the Trademark cream may be used safely with restrictions/precautions placed in labeling if the Sponsor adequately addresses the following prior to approval:

- 1) The Sponsor needs to conduct an adequate 21-day contact sensitization potential study of methyl-ALA and in the challenge phase test both ALA which is an endogenous metabolite (to rule out cross-sensitization) and methyl-ALA.
- 2) Provide data driven instruction for prevention of sensitization of healthcare professionals handling Trademark cream.
- 3) As part of labeling develop visual instructional material (e.g., video, CD, etc.) to ensure optimal safety and efficacy with use of the drug-device. The material should not be promotional in nature and submitted to the Agency for approval prior to distribution. The instructional material should include (but not limited to) dosage and administration procedures, and Adequate procedures to prevent cross contamination with between patient use of the device are also needed.
- 4) Provide the following information relative to labeling:
 - A. Identify types of gloves for which methyl-ALA and excipients found in TRADEMARK Cream will not penetrate.
 - B. Submit the line listings and serum transaminase level information for the patients

- treated with TRADEMARK Cream in the BCC study(ies).
- C. Describe lack of safety monitoring done in Phase 3 studies to preclude systemic adverse events as suggested in preclinical studies.
 - D. Provide the maximum duration of time permissible between application and illumination. Please provide information regarding needed adjustments to duration of light treatment following inadvertent prolonged exposure to TRADEMARK Cream before light exposure. Provide information regarding what a patient should do if there is prolonged exposure without subsequent light treatment - e.g. avoidance of sunlight for # days. All of these pieces of information should be supported with data and not hypothetically derived. As the disposition of methyl-ALA inside the body is not clearly known, please clarify the issue and provide supportive documentation.
 - E. It is unknown whether the risk of illumination after longer application periods (e.g., up to _____ with TRADEMARK Cream is warranted for the treatment of actinic keratosis. It is recommended that the cream should be rinsed off and illumination should be avoided. Labeling should be adjusted accordingly.
 - F. Provide instructions for what should be done with light overexposure - e.g. would management be similar to care for burns from other causes?
 - G. It is suggested that the Sponsor submit a Patient Package Insert to describe to patients the PDT procedure.
 - H. Provide information regarding the radiant heat and temperature achieved with skin surfaces exposed to the Curelight Model 01 device.
 - I. Provide information and rationale regarding how long the redness and swelling last before the patient should contact their doctor. This should be supported with data from studies.
 - J. Inform as to how long it takes for the surrounding skin reddening, swelling, crusting, blistering, edema, ulceration, peeling, itching and bleeding to resolve. Again, this should be supported with data.
 - K. Give actual percentages of patients with peeling, bleeding, itching and severe pain in patients aged 65 and older (being greater than that in younger patients).
 - L. Provide the number of patients treated with TRADEMARK Cream - the denominator for adverse events should not be diluted with vehicle or other treatments.
 - M. Calculate the percentages for adverse reactions based on occurrence(s) per patient. Also, please provide the upper 95% confidence interval.
 - N. Provide information regarding severity of burning sensation and skin pain seen in U.S. and Australian studies.
 - O. Identify the light transmittance through 1 millimeter of TRADEMARK Cream at 30^N C.
 - P. Please provide a list of anesthetics and the frequency with which they were used in Phase 3 studies.
 - Q. Identify the type of spatula used in clinical studies (e.g. what is the composition?).
 - R. Provide subgroup analysis with regard to wait time or information regarding compensatory calculations for lamp exposure during Curelight 01 light treatment.

- S. Adequate procedures to prevent cross-contamination with use of the device necessitates that the Sponsor provide a modification that is acceptable to the Agency for use of the device (Curelight 01 lamp) that would allow for adequate patient protection (i.e., Universal Precautions) and at the same time not hinder efficacious use.
 - T. Please provide information/description for treatment of multiple lesions - e.g., multiple lamps vs. single lamp, staggering of lesions, etc.
 - U. Provide information regarding effect of local anesthesia and increased pain intolerance on adverse events (i.e., were patients who were given local anesthesia more likely to have burns due to failure to feel discomfort and/or were they less likely to report local adverse events such as pain and stinging?).
 - V. Provide information regarding what should be done with the lesion area after exposure to red light treatment with the Curelight 01 lamp.
 - W. A visual aid should be submitted which would be part of labeling. The treatment process appears to be fairly complicated and such an aid should allow for safer (for both practitioner and patient) and more efficacious use of your drug/device).
 - X. Information on light and drug overdosage needs to be symmetrical and supported by data.
 - Y. Identify if _____ is appropriate to be placed under _____
- 5) The Sponsor should submit the clinical trial results of Study PC T212/00 which is a Phase 2 randomized, comparative phototoxicity study of Trademark cream vs. ALA 20% cream applied for 5 hours conducted in healthy individuals. Sponsor should submit a complete safety update including all safety data from other studies conducted with Trademark cream should be submitted.
- 6) Commit to conduct Phase 4 post-marketing studies. The Phase 4 post-marketing studies are listed below.
- A. Sponsor should agree, as a Phase 4 commitment, to conduct a 12-month study in at least 200 evaluable patients with 10 or more lesions (located on the face and scalp) have the following collected: hepatic transaminases (ALT and AST), alkaline phosphatase, total bilirubin, and complete blood count plus differential data at baseline and at one week after the second repeat dose 7-day regimen.
 - B. The Sponsor should agree to conduct a longer-term Phase 4 study documenting the effects of multiple retreatments and recurrence rate with its product. Actinic keratoses may be considered to be a chronic remittent disease and multiple retreatments are common, especially in older, sun overexposed patients.
 - C. The Sponsor should agree to conduct a Phase 4 study to determine the photoallergenicity potential of TRADEMARK Cream with a diluted form of TRADEMARK Cream.
 - D. The Sponsor should agree to conduct a safety and efficacy Phase 4 study of Metvix in patients of Asian or Hispanic heritage.
 - E. The Sponsor should agree to conduct additional Phase 4 studies as per the Pharm/Tox reviewer and Biopharm reviewer should also be agreed to by the Sponsor.
- 7) The following are informational needs that were forwarded to the Sponsor and are still outstanding. During conduct of the Phase 3 studies:
- A. Was there any patient discomfort associated with lesion preparation?
 - B. Did the investigators use anesthetics prior to lesion preparation?

- C. Did or should investigators use gloves during Metvix cream application?
- D. Is there any personnel protection instructions for inadvertent exposure to Metvix cream?
- E. Is Tegaderm® transparent or translucent, and what instructions were given to patients regarding restrictions during the 3-hour interval between Metvix application and removal?
- F. Did patients experience any AEs (e.g., burning, stinging, itching, etc.) during Metvix application prior to removal? If so, what was the remedy?
- G. What instructions were provided regarding use of 2 lamps? Was there a strategy developed for cream removal, avoidance of overlapping treatment fields, etc.? Should there be a limit to the number and location of treatment fields?
- H. What was the purpose for use of water spray and fan during illumination? Was this technique included in the protocol? What type of water spray was used and would use of a water spray disperse residual Metvix cream?
- I. Since the Sponsor did not provide disinfection/sterilization procedures, what techniques were employed by the investigators for between patient use of the device?
- J. Did the study nurse follow a triage protocol for referral to the sub-investigator for treatment of local adverse events?
- K. Who recorded local and systemic AEs at the following:
 - before and after each treatment session,
 - at 2 week post-treatment visit, and
 - 3-month efficacy endpoint visit?
- L. Were there post-treatment instructions provided for patients (e.g., restrictions immediately after treatment, remedies for possible AEs such as swelling, burning, crusting, etc.).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The study drug, methyl aminolevulinate hydrochloride is applied topically under occlusion to prepared actinic keratosis lesions and then illuminated with red light of wavelength 570 to 670 nm and total light dose of 75 J/cm² using the CureLight lamp. This drug-device combination involves a two-step process of lesion preparation/application plus illumination that is repeated in 7 days for treatment of mild to moderate nonhyperkeratotic actinic keratoses located on the face and scalp.

The Sponsor submitted results from four Phase 3 studies; however, the number of treatment sessions and patient population differed. Two studies (PC T306/99 and PC T305/99) although not identical are considered pivotal studies. Study PC T306/99 was conducted in the U.S. under IND 59,765 and the other, Study PC T305/99, was not conducted under the IND in Australia. Both PC T306/99 and PC T305/99 were multi-center, randomized, double-blind, parallel-group, vehicle-controlled clinical trials with use of Tradename-PDT for the treatment of mild to moderate, nonhyperkeratotic actinic keratoses located on the scalp and face. Study PC T305/99 included a cryotherapy study arm. Efficacy data from the cryotherapy arm of the study will not be used to support approval of the NDA. The U.S. study did not have a cryotherapy study arm and due to the nature of the treatment, blinding was non-existent after randomization. Additionally, the freezing time was inadequate (e.g., freeze time range was 2 seconds to 1 minute 30 seconds with a mean of 13 seconds).

Patients were male and female who were 31 to 86 years of age of Caucasian origin with Skin-Phototypes I-III. The study duration was only 3 months, re-treatment was not performed on lesions that did not completely respond to treatment, and recurrence rates were not evaluated.

Studies PC T 301/99 and PC T 302/99 were different from each other in study arms and different from the previously mentioned Phase 3 studies in treatment regimen and study population. The Phase 3 studies are summarized in the table that follows.

Overview of Phase 3 Trials

Study	Study (Study dates)	Lesion criteria	Treatment arms: (number enrolled)	Treatment Regimen
PC T306/99	US (6/00-2/01)	4-10 mild to moderate AK lesions on the face or scalp	Tradename PDT (42) Placebo PDT (38)	<u>Two</u> PDT-treatment sessions 7 days apart
PC T305/99	Australia (3/00-12/00)	Unlimited mild to moderate AK lesions on the face or scalp (limited to 6 treatment fields) and suitable for cryotherapy	Tradename PDT (91) Placebo PDT (23) Cryotherapy (90)	<u>Two</u> PDT-sessions with 7 days apart <u>Cryotherapy</u> : one treatment session with <u>one</u> freezing cycle
PC T302/99	Europe (6/99-1/00)	1-10 mild, moderate, or thick AK lesions on any location	Tradename PDT (20) Placebo PDT (19)	<u>One</u> PDT-session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations
PC T301/99	Europe (4/99-11/99)	1-10 mild, moderate, or thick AK lesions on any location and suitable for cryotherapy	Tradename PDT (102) Cryotherapy (100)	<u>One</u> PDT-session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations. <u>One</u> cryotherapy:-treatment session with two freezing cycles

B. Efficacy

In two Phase 3 clinical trials, two photodynamic therapy sessions conducted with Tradename Cream has shown superiority over vehicle (placebo) cream in treatment of actinic keratoses (p-value <0.001) at the 3-month efficacy endpoint. The two-stage process involves the following: (1) superficial preparation of the lesions followed by application of Tradename[®] 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 and total light dose of 75 J/cm² using the CureLight lamp. The entire two-stage process is repeated twice 7 days apart.

Efficacy of only one-treatment session for AK lesions located on the face and scalp was not substantiated by a second vehicle-controlled trial. Additionally, the sample size was small with only 37 (19 active and 18 placebo) patients evaluated for safety and efficacy and blinding was problematic in that during a portion of the trial, the caps on study medication tubes were color coded by content (active vs. vehicle). The remedy (independent review of photographs) to determine whether bias had been introduced indicated that bias had been introduced. Excellent response rates for clinical vs. photographic evaluations of 38% vs. 38% and 11% vs. 28%, active and placebo; respectively were reported. The Sponsor's rationale for discrepancies between the

two evaluations seemed logical in that thin AK lesions are better felt than seen and the results were influenced by the skewed distribution of thin and moderately thick lesions; however, photographic evaluation data were not submitted to the NDA.

C. Safety

Only 130 patients were exposed to the two-treatment sessions administered 7 days apart for AK lesions located on the face and scalp. No re-treatment safety data was generated and presented. A total of 201 patients (102 patients in Study 301 and 19 patients in Study 302) were exposed to one treatment session for AK lesions located on the face and scalp. Patients were assessed for efficacy 3 months after the last treatment session. The long-term safety data presented in the submission is limited to 30 patients treated with a different regimen.

Additional information received from the Sponsor suggests that the local AE profile presented for PDT treatment with TRADEMARK Cream may not provide an accurate profile as it relates to burning, skin pain, stinging, and pruritus. The Sponsor should have considered use of anesthetics and analgesics as an integral part of the procedure if the degree of discomfort is rather intolerable for patients. The need to anesthetize the treatment area prior to treatment was not addressed in the protocol.

According to a faxed communication received from the Sponsor on July 24, 2002, during training sessions investigators were instructed not to use local anesthetics, except in special cases when specifically requested by the patient. In the Australian study, 14% (12 of 88) patients on active-PTD received local anesthetics and 18% (16 of 88) received topical or oral analgesics. None of the vehicle-PDT patients received local anesthetics or analgesics. In the U.S. study, 2% (1 of 42) patients on active-PTD had local anesthetic administered and 11 received analgesics while for the vehicle-PDT study arm, 14% (5 of 38) had local anesthetics administered and 1 received analgesics.

The use of local anesthetics may have masked the intensity of AEs such as burning and stinging if administered prior to red light illumination. Use of local anesthetics prior to the second treatment session coupled with analgesic use, might explain the decrease in local AE reported for the second treatment session. Adverse events with intensities that were deemed moderate to severe were listed as burning, erythema, skin pain, stinging skin crusting, skin edema, blisters, peeling skin, bleeding skin, skin ulceration, itching, pruritus, and skin infection. Symptoms such as burning, skin pain, stinging, and pruritus may have been under-reported secondary to masking of symptoms; therefore, an accurate profile with use of this drug is unknown.

In the U.S. study, local adverse events were assessed and recorded at each treatment session and assessed 2 weeks after the second treatment session by the study nurse who administered the light treatment. Patients were referred for treatment of adverse events at the discretion of the study nurse and the Sponsor did not indicate that there was a triage protocol for this procedure. According to a faxed communication from the Sponsor, the study nurse recorded both local and systemic adverse events. It was not stated whether a physician reviewed these results. In the Australian study, adverse events were monitored and recorded by the investigator. No systemic laboratory monitoring was conducted during any of the Phase 3 studies.

Most adverse events in Tradename group were local adverse events. Among them, 99% of the events (i.e. 298/301) were considered treatment-related and most were mild to moderate in severity. Two subjects (1.5%) in Tradename group discontinued the treatment due to adverse events. Burning sensation skin and erythema were the most common local adverse events for Tradename and placebo PDT (23%, 21% in Tradename and 18%, 27% in placebo).

According to the Sponsor, the outcome of all related local adverse events reported by $\geq 1\%$ of patients with intensities that were moderate or severe resolved. Two cases with moderate erythema in Study 305/99 and 1 severe case of erythema in Study 306/99 in the Tradename-PDT treatment group persisted. Summary table of local adverse events follows.

Adverse events in the table that follows are tabulated as the percentage relative to total local AEs and as previously discussed may not provide an accurate AE profile. The Sponsor has been asked to calculate the percentages for adverse reactions based on occurrence(s) per patient.

Summary of Local Adverse Events

Events	Tradename PDT (n=130)	Placebo PDT (n=61)
Subjects with at least one adverse event	114 (88%)	33 (54%)
Total adverse events	488	76
Total local adverse events	301	44
# of local adverse events:		
Burning sensation skin	70 (23%)	8 (18%)
Erythema	64 (21%)	12 (27%)
Crusting	20 (7%)	6 (14%)
Pain skin	29 (10%)	3 (7%)
Blisters	14 (5%)	2 (5%)
Edema skin	21 (7%)	1 (2%)
Stinging skin	25 (8%)	2 (5%)
Skin ulceration	7 (2%)	0
Skin peeling	14 (5%)	2 (5%)
Pruritus	8 (3%)	2 (5%)
Itching	9 (3%)	0
Bleeding skin	11 (4%)	2 (5%)
Irritability skin	1 (< 0.5%)	0
Milia	1 (< 0.5%)	0
Hyperkeratosis	0	1 (2%)
Skin infection	3 (1%)	1 (2%)
Dermatitis contact	1 (< 0.5%)	0
Photosensitivity toxic reaction	1 (< 0.5%)	0
Rosacea	1 (< 0.5%)	0
Skin hyperpigmentation	1 (< 0.5%)	0
Skin disorder	0	1 (2%)
Skin inflammatory NOS	0	1 (2%)
Source: Sponsor's NDA submission (pages 97-99, Volume 42; pages 57-58, Volume 45).		

No deaths were reported in patients enrolled in the placebo-controlled studies. Two deaths were reported in patients enrolled in the cryotherapy study arm. Five deaths were reported in patients exposed to Tradename Cream in other studies; however, none were considered treatment related.

The causes of death were listed as heart failure, pulmonary infarction, malignant metastatic melanoma, pneumonia, and kidney neoplasm. One additional death in a patient enrolled in ongoing BCC study 310/00 died of systemic infection that occurred during hospitalization for a below-knee amputation and the relationship to treatment is listed as unknown.

Three patients discontinued during the placebo-controlled trials, all enrolled in the active study arm. Two of 149 (1%) patients in the active-arm discontinued treatment before the second treatment due to adverse events and one of these was lost to follow-up. One of the discontinued study participants, Patient #4010, suffered a second-degree burn after one-treatment session. One patient discontinued illumination during the first treatment and withdrew consent.

Unresolved Safety Issues

The quality and quantity of safety database submitted with the NDA does not include enough information to exclude possible safety issues for the proposed dosing regimen. New data submitted for the first time at NDA submission and new information resulting from queries made by the Division during NDA review has made it evident that additional safety data is needed in order to make an informed risk benefit assessment for review purposes.

1) The Sponsor was advised that assessment of safety should include changes in laboratory parameters and if not included an adequate rationale for excluding this data should be presented by the Sponsor. A rationale for not assessing changes in systemic laboratory monitoring was not provided in the NDA; however, according to the Sponsor (Vol. 1.22, pg. 20), pre-clinical studies suggest negligible systemic absorption of radiolabelled methyl 5-aminolevulinate. The Sponsor did submit systemic laboratory data from 359 patients in Studies 202/98, 303/98, 204/98, and 205/98. These data were not obtained from patients treated at the proposed dosing regimen of two treatment sessions 7 days apart (see discussion under Adequacy of Safety Testing)

- According to Pharm/Tox Reviewer, non-clinical data submitted for the first time with the NDA suggests that there may be potential for systemic exposure to methyl ALA after repeated treatments that may result in adverse effects on the liver and blood. It is this reviewer's understanding (verbal communication) that if these Pharm/Tox non-clinical study results had been reviewed by the Division prior to conduct of the Phase 3 clinical studies, systemic laboratory monitoring in humans during conduct of Phase 3 clinical trials would have been suggested. A clinical trial with only 3-month follow-up safety data may have been insufficient to clinically detect adverse effects on the liver and hematological parameters without laboratory monitoring.
- Additionally according to the Biopharm Reviewer, the Sponsor has not adequately assessed the in vivo bioavailability of methyl-levulinic acid or levulinic acid (the active form of methyl-levulinic acid).
- No systemic pharmacokinetic data in humans are available. Due to putative instability of the methyl-ALA in serum, no pharmacokinetic studies have been conducted *per se*. Instead, photoactive porphyrins (PAP) fluorescence was used to assess the PK of methyl-aminolevulinate HCl in studies PC T101/97 and PC T206/99. Additionally, the PK studies were not conducted under maximal usage conditions and the maximal amount of cream studied was 1 gram of Trademark cream. The amount of Trademark cream applied during conduct of the Phase 3 studies was not provided and it is unknown whether the Sponsor collected these data.

- The treatment regimen selected by the Sponsor enhances penetration and increases the risk for systemic exposure to Trademark cream. The risk of systemic exposure is enhanced by: 1) lesion preparation (e.g., removal of crust, scale, etc. with a dermal curette), 2) repeat treatment within 7 days, and 3) use of the highest drug concentration
- Laboratory data submitted from 30 patients enrolled in the 3 h, 160 mg/g study arm of an open dose-ranging study was obtained one week after one treatment session. Although no laboratory abnormalities were noted in this small sample, there was no vehicle study arm, the dosing regimen is different and is insufficient due to the small number of subjects studied. Incomplete laboratory data from patients enrolled in an ongoing basal cell carcinoma study consisted only of scatter plots plotted against baseline at 2 and 7 weeks after the first treatment for serum ALAT, ASAT and bilirubin values. Full data sets were not submitted for review.
- 2) In addition to recurrence rate and long-term safety, re-treatment data are needed since recurrent and new lesions requiring treatment can be expected. The methyl ester of ALA appears to be a potent contact sensitizer. The Sponsor admits to a possible contact sensitization potential confirmed by re-challenge results of 3 subjects studied. In addition to the patient, the healthcare provider is also at risk for developing contact sensitization since TRADEMARK Cream is applied in the office after lesion preparation and not applied by the patient.
- A provocative cumulative irritancy and sensitization (allergenicity) study was conducted in 25 healthy adult subjects (usually 200 subjects are studied) randomized and tested with TRADEMARK Cream and with vehicle cream. After only 9 days (usually these provocative tests are done over 21 days, but the test was stopped at 9 days), seventeen out of the 25 (68% with an upper 95% confidence boundary of 85%) subjects had definitive erythema and irritation (score greater than 0) with TRADEMARK Cream without occlusion vs. 1 out of 25 with this reaction to the vehicle at the end of the irritation phase. In the challenge phase, 5 out of the 25 subjects (20% with an upper 95% confidence boundary of 40%) had reactions consistent with a topical sensitization (allergic) reaction. Rechallenge was done 3 weeks later and 3 out of 4 patients tested had a positive reaction (75% with an upper 95% confidence boundary of 99%). Because the first part of this provocative testing was done only for 9 days, TRADEMARK Cream may be even more irritating and sensitizing (causing skin allergies) than evidenced from this study.
- The Sponsor acknowledges that the potential to elicit skin sensitization is relevant; however, the Sponsor's contention that in most cases a "single" occasion treatment is expected (ISS, Vol. 1.37, pg. 182) is unrealistic. Typically, actinic keratoses begin to appear in the fourth and fifth decades, and increase in number in the advancing years. Since re-treatment or additional treatment is expected contact sensitization is a concern that should be addressed.
- Contact sensitization was not observed in a similar ALA drug product (Levulan) that does not contain a methyl group. Cross sensitization potential between the already approved ALA product is unknown. Cross sensitization with endogenous ALA is unknown and is a concern. Sensitization of the medical personnel administering TRADEMARK Cream is also a concern and needs to be addressed by the Sponsor.
- Additional information is needed regarding contact sensitization potential of TRADEMARK Cream, cross sensitization with ALA, contact photoallergenicity of TRADEMARK Cream, and types of gloves for which the methyl-ALA and excipients found in TRADEMARK cream will not penetrate for use by the healthcare professionals handling the medication.

- 3) Phase 3 safety database consists of only 130 patients exposed to active drug at the proposed dosing regimen. The Phase 3 protocol was not designed to provide re-treatment data and there was only 3 months follow-up. According to the pre-IND meeting minutes, the Sponsor was strongly encouraged to modify the proposed Phase 3 protocols to permit assessment of recurrences in treated patients after 12 months. The Sponsor was advised that it was not clear whether the results from Phase 2 Study 202/98 could be extrapolated to the Phase 3 studies if there were substantial differences in study design between the Phase 2 and Phase 3 protocols.
- To support long-term follow-up, the Sponsor submitted data from study PC T 202/98, an open exploratory (Phase I/II) study of Tradename Cream 80 mg/g and 160 mg/g applied for 1 or 3 hours in patients with primary AKs. In this study, recurrence was assessed at month 12 in all lesions, which had shown complete response in the previous evaluation: however, it is not clear how lesion identification was ascertained at the 9 or 12-month follow-up. Only 30 patients were treated with 3h application at 160 mg/g concentration. Twenty-nine of these patients were evaluable for recurrence and 28 patients completed follow-up.
 - Data from Study PC T202/98 can not be extrapolated to the Phase 3 studies to provide adequate long-term follow-up since the treatment regimen was different (if administered, the second treatment was conducted 2 months after the first treatment session). The Sponsor should agree to conduct a Phase 4 safety and efficacy study to measure the recurrence rate of actinic keratoses treated with its product.
- 4) The quality and reliability of systemic as well as the local AE data collected in the U.S. study (306/99) may not be reliable in that these data may not have been collected based on observations of a qualified investigator. Additionally, the use of local anesthetics and analgesics (topical or oral) may dilute the intensity reported for some AEs in the pooled safety data. This use of local anesthetics and analgesics perhaps explains the lower incidence of reported AEs for the second treatment session.
- According to a faxed communication received from the Sponsor on July 24, 2002, during training sessions investigators were instructed not to use local anesthetics, except in special cases when specifically requested by the patient. These were recorded as concomitant medications. In the Australian study 305/99, 14% (12 of 88) patients on active-PTD received local anesthetics and 18 % (16 of 88) received topical or oral analgesics. None in the vehicle-PDT group (0 of 23) received local anesthetics or analgesics (topical or oral). In the U.S. study 306/99, 1 of 42 patients on active-PTD had local anesthetic administered and 11 received analgesics while for the vehicle-PDT study arm, 5 of 38 had local anesthetics and 1 receive analgesics.
 - In the U.S. study, local adverse events were assessed and recorded at each treatment session and assessed 2 weeks after the second treatment session by the study nurse who administered the light treatment. Patients were referred for treatment of adverse events at the discretion of the study nurse and the Sponsor did not indicate that there was a triage protocol for this procedure. According to a faxed communication from the Sponsor, the study nurse recorded both local and systemic adverse events. It was not stated whether a physician reviewed these results. In the Australian study, adverse events were monitored and recorded by the investigator.

- Adverse events should have been presented separately to assess drug effect alone from PDT for each of three time periods (during drug application, illumination, and post-treatment) as to the type and quantity of the adverse event. AEs resulting from the curettage procedure should have assessed separately.
 - In the majority of cases, local adverse events were considered related to study treatment. The Sponsor only presented related local adverse events; however, all AEs should have been reported. Adverse events collection in the Case Report Form was not limited to treatment related AEs; therefore, the Sponsor should provide a listing of all reported AEs. The percentage for adverse reactions based on occurrence(s) per patient with the 95% confidence interval should be provided.
- 5) Phase 3 studies are to simulate as closely as possible post-approval use; however, to this reviewer, the actual conduct of these studies were not as per the written protocol. The technique was demonstrated to each investigator and apparently this significantly supplemented the written protocol.
- For the Australian study, treatment fields were recorded and up to 6 field per patient were permitted per protocol yet the majority of patients had less than 4 lesions. The number of treatment fields was not restricted in the U.S. study (306/99) where all patients had 4 –10 lesions. The Sponsor did not present a strategy, perhaps staggering the application of cream to various groups of lesions when a patient has many, as encouraged Division. There are no precautions, efficacy or safety data regarding overlapping treatment fields or the necessity of overlap avoidance.
 - The illumination time presented in the NDA represents per lesion totals. According to the data submitted, application time ranged from 2:10 - 4:45 (active) and 2:56- 4:28 (placebo). According to the protocol, a total application time of 32 hours was acceptable. The Sponsor did not assess the effect of length of application time on safety and efficacy. The Sponsor did provide the maximum duration of time permissible between application and illumination. Information regarding needed adjustments to duration of light treatment following inadvertent prolonged exposure to TRADEMARK Cream is needed. Information regarding what a patient should do if there is prolonged exposure without subsequent light treatment – e.g. avoidance of sunlight for # days – supported with data and not hypothetically derived should be provided. As the disposition of methyl ALA inside body is not clearly known the Sponsor is asked to clarify the issue and provide supportive documentation.
 - Tegaderm is not opaque and the Sponsor asserts that no special precautions were necessary in the 3-hour period between cream application, removal, and illumination. However, data were not collected in a manner during conduct of Phase 3 studies (e.g., AEs collected prior to application, after removal of Trademark cream, and prior to illumination) that would substantiate this claim.
 - Visual instructional material (e.g., video, CD, etc.) should be developed and distributed with the drug product to ensure optimal safety and efficacy with use of the drug-device. The material should not be promotional in nature and submitted to the Agency for approval prior to distribution. The instructional material should include (but not limited to) dosage and administration procedures, and Adequate procedures to prevent cross contamination with between patient use of the device are also needed and are addressed below.

6) Although considered a device issue, adequate procedures to prevent cross-contamination with use of the device necessitates that the Sponsor provide an acceptable modification to the use of its device that would allow for adequate patient protection (i.e., Universal Precautions) and at the same time not hinder efficacious use. Procedures used by individual investigators for between patient sterilization during conduct of the Phase 3 studies not known. According to the Sponsor, sterilization instructions were not provided to investigators and there have been no reports of cross-contamination between patients. FDA Microbiology Reviewer states that instructions for between patient sterilization of the device used in this study are inadequate. This safety issue remains unresolved at the time of the written review. CDRH will be working to resolve this and approval of the Device should be pending resolution of that safety concern. The final approval of this product, which is only indicated for use with the specific light-emitting device under consideration at CDRH, is pending approval of the use of the device.

- The Sponsor has proposed

- The Division is recommending that a clear covering be used on the diode thereby eliminating _____ of patients. Additionally for horseshoe-positioning device, use of an appropriate disposable cover is also recommended since the placement of the horseshoe-positioning device on intact epidermis cannot be guaranteed in patients with multiple AKs that have been prepared for therapy.
- If the Sponsor agrees with the suggestion to use a clear covering to insure non-transfer of infectious material, the Sponsor will need to address the following:
Demonstrate that the material does not significantly alter light transmittance. This can be done by making measurements using the calibration probe with and with out the covering material over the light receptor. The difference in transmission should be easily detected by this method.
 - ◆ Use animal models to test with the covering material in place for representative lengths of time relevant to clinical use to see if it produces a heat problem that results in formation of a moisture barrier.
 - ◆ Provide a revised operator manual clearly specifying dosimetry/calibration and treatment with such a barrier in place.
 - ◆ Discuss/ address the issue of treating multiple AK's in terms of side by side lesions and how to prevent light field overlapping if the lesions are close to each other but can not be treated in a single field.
 - ◆ Provide a discussion regarding the horseshoe shaped position device in terms of what its intended use is. Is this for determining distance to insure correct spot size or does it have some function regarding centering of lesion? Is the device designed so that it has an acceptable excess of area to allow sufficient normal skin

remaining around the lesion?

6) The Sponsors proposed name of "Metvix" has been found not to be acceptable by Agency reviewers in the Office of Drug Safety. The Sponsor will need to propose a new tradename for review prior to marketing this product. The product, when and if approved, may still have this issue outstanding.

D. Dosing

According to the Biopharm reviewer, an intermediate concentration (between 80 and 160 mg/g for 3 h) may work as well with less potential for adverse events.

E. Special Populations

Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

In vehicle-controlled studies, there was higher incidence (a $\geq 10\%$ difference) in females than in males in the same treatment arm for the following adverse events: skin pain, stinging skin, crusting, blisters, and pruritus. For the overall Tradename experience (AK and BCC), the Sponsor concluded that the number of adverse events were similar in male and female patients on active drug.

Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Evaluation of Evidence Age (safety)

In the vehicle-controlled studies, a total of 229 patients comprised the safety population for the actinic keratosis indication. Of the 229 patients enrolled, 149 patients were assigned to the Tradename Cream study arm and 80 (54%) of the patients receiving Tradename Cream were ≥ 65 years of age. . No difference was noted in efficacy between patients that were younger than 65 years and those 65 years and older.

According to the Sponsor's analysis of local adverse events reported by $\geq 1\%$ of all patients in vehicle-controlled AK studies, there is a $\geq 10\%$ between age group difference for peeling skin, bleeding skin, and itching as compared to patients ≤ 65 years of age. There also was a tendency towards severe skin pain patients ≥ 65 years of age.

Overall Tradename Cream adverse events experience (AK and BCC) was presented for incidence of adverse events in AK and BCC studies by patient age group in the safety population (Vol. 1.37, pg. 158 & 159). According to the submission, a total of 753 patients were treated, with 560 (74%) patients reporting adverse events. Of the 560 patients a total of 354 (73%) reported local AEs and 95 (20%) reported non-local AEs.

The Sponsor concluded that generally, the results were similar for both age groups except that there was a $\geq 10\%$ difference in erythema in patients with BCC (57% in patients < 65 and 47% in patients > 65 years of age. The results suggest that the profile of local and non-local adverse events did not differ between < 65 years and ≥ 65 years of age.

Evaluation of Evidence for Race or Ethnicity Effects

All patients in the vehicle-controlled studies were Caucasian with photo-skin Types I-III. Of these the number of patients with skin Type III or higher was low (N=19). The incidences of non-local AEs for patients treated with Tradename Cream were similar for all skin types studies.

The safety profile of Tradename-PDT treatment in other ethnic groups (e.g., Hispanics, Asians) who are at lower risk, but not zero risk for development of actinic keratoses is needed.

Evaluation of Pediatric Program

Actinic keratosis occurs very rarely (although unknown, the estimated occurrence less than 1 in 10,000) in the pediatric population; therefore, the Sponsor is requesting a waiver of the requirement to assess the effects of Tradename Cream in pediatric patients 16 years and younger. Such a waiver is appropriate for this product when used for this indication.

Use in Pregnancy

Reproductive studies in animals have not been performed and the drug is labeled as Pregnancy Category C. One patient is known to have become pregnant, with probable conception beginning at least 2 months after receiving Tradename-PDT. The outcome was reported as uneventful.

APPEARS THIS WAY
ON ORIGINAL

CLINICAL REVIEW of NDA 21-415

Clinical Review Section

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

- Established Name: Methyl aminolevulinate hydrochloride
- Proposed Trade Name: Tradename® Cream
- Sponsor's Proposed Indication: Non-hyperkeratotic Actinic Keratoses
- Proposed Dose/Regimen: (1) superficial preparation of the lesions followed by application of Tradename® 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 and total light dose of 75 J/cm² using the CureLight lamp.

B. State of Armamentarium for Indication(s)

Actinic keratoses (AKs) 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. Current therapy for AK include cryosurgery, electrodesiccation and curettage, topical application of 5-fluorouracil (5-FU), or recently approved photodynamic therapy with Levulan® Kerastick™ (aminolevulinate hydrochloride).

C. Important Milestones in Product Development

Regulatory Background

- Pre-IND Meeting, August 2, 1999
- Teleconference on Device Section, May 3, 2000 ()
- End-of-Phase 2 Meeting, June 22, 2000
- Teleconference on Device Section, November 17, 2000 ()
- Biopharmaceutical Teleconference, January 31, 2001
- Pre-NDA Meeting, May 2, 2001

Pertinent regulatory history pertaining to the development of the NDA

Notable issues discussed during the Pre-NDA Meeting for IND 59,756 held between the sponsor and the Division on May 2, 2001 are as follows:

- One of two of the controlled studies, Study PC T305/99, was conducted in Australia. This study had not previously been communicated to the Agency and that the Agency lacked information about the protocol, declared method of analysis, or its investigators. Acceptability of the study would be a review issue since the Agency had no information about this protocol. Additionally, a trial conducted in a foreign country is subject to the regulations outlined in 21 CFR §312.120 and §314.106.

- The potential for allergenicity/sensitization needs to be determined before NDA submission unless the product is already known to be allergenic. If such information is not yet available, such studies typically include 200 subjects.
- Assessment of safety should include reasonably frequent physical examinations by the principal investigator, with review of adverse events, evaluation of photodynamic effects (i.e. erythema, edema, burning/stinging, wheal, vesiculation, hemorrhage, ulceration, necrosis, scaling, crusting and itch) pigmentary changes and changes in laboratory parameters. Protocol should include monitoring for systemic toxicity, or an adequate rationale for excluding this data should be presented by the sponsor.
- It was not clear whether the long-term efficacy results from the Phase 2 study conducted by the Sponsor could be extrapolated to the Phase 3 studies if there are substantial differences in the study design between the Phase 2 and Phase 3 studies. The Sponsor was strongly encouraged to modify the proposed Phase 3 protocol to permit assessment of recurrence in treated patients after 12 months. The Agency indicated that it would engage in internal discussion to resolve whether an NDA containing 3-month follow-up after treatment would be fileable.

D. Other Relevant Information

This is a drug-device combination in which methyl aminolevulinate hydrochloride (methyl-ALA) is used only in conjunction with illumination with the PhotoCure lamp (Model: CureLight 01) in treatment of non-hyperkeratotic actinic keratosis. The device, Model: CureLight 01, is reviewed separately by CDRH. See Dr. Richard Felton's review of the device.

Tradename Cream contains methyl aminolevulinate hydrochloride (methyl ALA), which is a methyl ester of aminolevulinic acid. The metabolism of aminolevulinic acid (ALA) is the first step in the biochemical pathway resulting in heme synthesis. Aminolevulinic acid and methyl ALA are not photosensitizers, but rather a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. The synthesis of ALA is normally tightly controlled by feedback inhibition of the enzyme, ALA synthetase, presumably by intracellular heme levels. ALA, when provided to the cell, bypasses this control point and results in the accumulation of PpIX (a photoactive porphyrin), which is converted into heme by ferrochelatase through the addition of iron to the PpIX nucleus.

According to the presumed mechanism of action, photosensitization following application of Tradename (methyl aminolevulinate) Cream occurs through the metabolic conversion of methyl ALA to photoactive porphyrins, which accumulates in the skin to which Tradename (methyl aminolevulinate) Cream has been applied. When exposed to light of appropriate wavelength and energy, the accumulated photoactive porphyrins produces a photodynamic reaction, a cytotoxic process dependent upon the simultaneous presence of light and oxygen. The absorption of light results in an excited state of the porphyrin molecules, and subsequent spin transfer from photoactive porphyrins (PAP) to molecular oxygen generates singlet oxygen, which can further react to form superoxide and hydroxyl radicals. Photosensitization of actinic (solar) keratosis lesions using the Tradename Cream, plus illumination with the Curelight Lamp (a red light of 570 to 670 nm wavelength, is the basis for Tradename photodynamic therapy (PDT).

Foreign experience

On June 26, 2002, the Agency was notified that Tradename® Cream has been approved for sale in both Sweden and Norway. Tradename® Cream had not been marketed as of September 2001 according to the original NDA submission.

On June 15, 2001, PhotoCure received the first marketing authorization in Sweden for photodynamic therapy with Tradename (Tradename-PDT) for treatment of actinic keratoses and basal cell carcinoma. Marketing authorization applications have been submitted for the same indication to the following countries:

Table 1 (Vol. 1.1, pg. 158): Marketing Authorization

Country	Date of Submission*	Status
---------	---------------------	--------



Post-Marketing Experience

Tradename® Cream has only recently been approved for sale in Sweden and Norway (note: the Sponsor did not provide the date of approval; however as per the original NDA submission, Tradename® Cream was not marketed as of September 2001). Post-marketing adverse events are reported to the MPA (Swedish Health Authorities), then the MPA forwards the reports to PhotoCure ASA. The same procedure applies to Norway. According to a submission received from the Sponsor on 06-28-02, to date, no AEs from these countries have been reported to PhotoCure ASA.

Applicability of Foreign Data to the U.S. Population and U.S. Medical Practice

The data submitted to support the NDA is predominately based on foreign data but not solely since Study PC T306 was conducted in the U.S. According to the Sponsor (Vol. 1.68, pg. 222), foreign data generated from the studies are applicable to the U.S. population with AKs. Among the rationale for applicability to the U.S. population, the Sponsor stated that AK is the same disease entity in Europe, Australia, and the U.S. Patients are generally Caucasians with fair complexion, over 40 years of age, and present with AK lesions in skin areas that have been chronically exposed to the sun. The lesions are due to chronic skin damage induced by sunlight and have characteristic histology.

There are no formal registry data on the incidence and prevalence of AK in different geographic areas; however, studies have shown that people with the highest UV exposure based on their occupational and/or recreational patterns are at greatest risks of developing actinic keratosis. The Sponsor states that the Caucasian population in the U.S. is similar to that of Australia and Europe and those in the southern U.S. would resemble that of the Australia and more northern U.S. would resemble northern Europe with less sun exposure.

Additionally, the diagnosis in the U.S. as well as Europe and Australia is usually made by dermatologists on clinical grounds by inspection and palpation. Biopsy is usually reserved for cases in which there is doubt about the diagnosis and for recurrent lesions when again the diagnosis must be questioned, in particular when squamous cell carcinoma must be ruled out.

E. Important Issues with Pharmacologically Related Agents

Aminolevulinic acid (ALA) is present in man and is present in both the mitochondria and cytoplasm of hemoglobin producing cells and in the liver. Tradename Cream (methyl aminolevulinic HCl) is an ester of ALA. A recently approved ALA drug product (Levulan®) is similar; however, does not contain a methyl group.

Cross sensitization between the already approved ALA product are unknown. Unlike Levulan® in which no contact sensitization potential was detected, an unexpected contact sensitization potential of up to 30% (upper 95% confidence limit) was demonstrated in 12% (3/25) of subjects studied in a 9-day induction period vs. the usual 21-day induction period. Cross sensitization with endogenous ALA although thought to be unlikely is unknown and is a concern.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews**A. Chemistry**

The CMC Review has not been completed, as a final inspection has not been performed; however, preliminary recommendation is approvable.

B. Animal Pharmacology and Toxicology

The Pharm/Tox Reviewer recommends that from a pharmacology/toxicology standpoint, the application is approvable. The recommendation is that tissues collected in the repeated dose dermal toxicology study in minipigs should be evaluated histologically. At a minimum, the kidneys, liver, spleen, thyroid and bone marrow should be evaluated.

Of significance is new data that suggests possible systemic toxicity from dermal application. A repeat dose minipig study was requested at the end of Phase 2 meeting to support the Sponsor's Phase 3 clinical trials; however, the report was submitted for the first time with the NDA. According to the Pharm/Tox Review, in a 14-day study in rats receiving daily intravenous doses of methyl ALA, increased liver weights were seen at all doses (50-600 mg/kg). At the high dose, equivalent to a human dose of 100 mg/kg or 15 times the maximum clinical dose, increased bilirubin, increased serum ALT, and cholangitis/peri-cholangitis were found.

In a study in rats of topically applied methyl ALA as TRADEMARK cream or dilutions thereof, followed by photoactivation and repeated for four treatments at intervals of 10-18 days, increased serum alkaline phosphatase and inflammatory foci in the liver were seen at all doses (60-600 mg/kg). Decreased serum protein and either gross liver enlargement or increased liver weight were seen at 300 and 600 mg/kg. At the high dose, using the clinical TRADEMARK formulation, equivalent to 100 mg/kg or 15 times the maximum clinical dose, serum ALA concentrations were ten-fold higher after the fourth dose than after the first dose.

A study of topically applied TRADEMARK cream followed by photoactivation and repeated for four treatments at intervals of 12-26 days was performed in a small number of minipigs. The applied dose was equivalent to at least five times the maximum clinical dose. Findings were suggestive of effects on the liver, but were inconclusive due to small sample sizes and incomplete evaluation.

According to the review, after the fourth treatment, thrombin time was higher in treated males than in control males, and serum ALT was higher and blood glucose was lower in treated males than in control males. These values were within the range of historical controls for the laboratory and were considered to be incidental findings by the Sponsor. However, they are consistent with signs of systemic exposure observed in the Sponsor's studies in other species.

According to the reviewer, due to the small sample sizes and age of the animals, organ weights were too variable to be informative. No toxicokinetic monitoring or histopathologic examination was performed. The dose of the test article was 2 g (average body weight was 6.5 kg, so approximately 300 mg/kg of drug product; HED=approximately 200 mg/kg of drug product) applied to a 50 mm diameter site (area approximately 1962 square mm, or 20 square cm), or approximately 100 mg per square cm. This would appear to be too thick an application and an overestimate of the actual dose that was in contact with the skin and available for absorption.

C. Biopharmaceutics

See Biopharm review for details of the PK studies.

Data from 2 clinical studies were submitted that investigated the penetration and accumulation of PAPs in lesions and normal skin of patients with AK and BCC, Study PC T101.97 and PC

T206/99. The Biopharm Reviewer recommends 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 Tradename Cream. At this time the applicant has not adequately assessed the in vivo bioavailability of methyl-levulinic acid or levulinic acid (the de-esterified form of methyl-levulinic acid).

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

D. Statistics

The Biometric Reviewer concluded that the efficacy claim of two sessions of Tradename PDT in the treatment of mild to moderate actinic keratoses (AK) lesions on the face or scalp is supported in two Phase 3 studies, PC T305 and PC T306, in terms of the percentage of subjects with 100% of all lesions cleared.

The Biometric Reviewer concluded that the efficacy claim may be supported in study PC T302, depending upon the number of baseline AK lesions considered in the labeling. However, for study PC T301, it is not possible to get a reliable estimate of the treatment effect, as no placebo arm was included.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

Due to instability of the methyl-ALA in serum, customary pharmacokinetic studies have not been conducted. Instead, photoactive porphyrins (PAP) fluorescence was used as surrogate to assess the PK of methyl-aminolevulinat e HCl in studies PC T101/97 and PC T206/99. According to the Biopharm reviewer, the fluorescence methodology was "not rugged" and not validated.

It should be noted that in PK Study 101/97 lesions were not prepared before treatment (no rationale was provided); however for PK Study PC T206/99, lesions were prepared as in the Phase 3 clinical trials. According to the Sponsor (Vol. 1.21, pg. 69), measurements of serum concentrations of 5-ALA and PAP were planned. However, the assays were not performed because 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-ALA could be expected to penetrate the skin in patients. If collected, adverse events were not reported for these PK studies. No systemic adverse events were measured and no rationale was provided.

B. Pharmacodynamics

This submission includes dermal safety studies on irritancy and allergic sensitization potential conducted on 25 subjects instead of 200 subjects. The results are discussed in Dermal Safety Studies Section.

IV. Description of Clinical Data and Sources

A. Overall Data

This review is based primarily on data submitted by the Sponsor. Seven clinical trials (four Phase 3, one Phase 2, and 2 PK studies) were conducted by the Sponsor to support use of photodynamic therapy with Tradename®168 mg/g cream in patients with actinic keratosis (AK). The Sponsor submitted data from the following studies:

- Two Phase 1 safety studies, Study PC T107/01 and Study PC T108/01 studied acute irritancy and cumulative skin irritancy and sensitization potential respectively.
- Two studies of the pharmacokinetics of methyl-aminolevulinate hydrochloride (Study PC T101/97) and photoactive porphyrins (PAP) (Study PC T206/98) were conducted.
- One open Phase 1/2 dose-finding study (Study PC T202/98) that included recurrence and safety data after 12 months was conducted.
- There were four Phase 3 studies, of which three were placebo-controlled (PC T305/99, Study PC T306/99, PC T301 and PC T 302).

B. Tables Listing the Clinical Trials

The Phase 2 dose ranging study and Phase 3 clinical trials conducted by the Sponsor follows:

Table 2 (Modified Sponsor's Table 1, Vol. 1.36, pg. 16): Table of Studies in the ISE

Study Number Start Date/ End Date Report Status	Country/ Coordinating Investigator	Population Studied	Design Type of Control Blind	Dose(s) and Frequency of Dosing	Treatment Duration (does not include follow-up period)	No. Pts. Treated Age range (mean) (years). Fitzpatrick skin type	Sex; Race (Caucasian, Non-Caucasian Unknown)
Phase II, Dose-Ranging							
PC T202/98 Aug 1998 to Mar 2000 Final	Switzerland, Norway, Netherlands, Sweden, Finland, Germany (Switzerland)	Patients with mild, moderate, or severe AK lesions in any location Unlimited number of lesions per patient	Phase I/II, open, randomized, parallel-group, multi-center, dose-finding	Tradename 80 or 168 mg/g for 1 or 3 hours before illumination with a light dose of 75 J/cm ² (wavelength 570 to 670 nm)	Repeat treatment at 2 to 3 months, if required	112 43-91 (73) Fitzpatrick skin type not assessed	63M, 49F 112 C
Active-Controlled, Phase III							
PCT 301/99 Apr 1999 to Nov 1999 Final	Switzerland, Germany, Austria, Italy, Netherlands (Switzerland)	Patients with mild, moderate, or severe lesions in any location 1-10 lesions per patient	Phase III, open, multi-center, randomized, stratified, parallel-group, comparative vs cryotherapy	Tradename : 168 mg/g or placebo for 3 h before illumination with a light dose of 75 J/cm ² (wavelength 570 to 670 nm) Cryotherapy: liquid nitrogen spray Two freeze thaw cycles	Tradename - 1 or 2 applications: Single treatment for lesions on face and scalp Second treatment session after 1 week for lesions at other locations Cryotherapy: single treatment	202 42-89 (71) Skin Type I: 10 (5%) Skin Type II: 133 (66%) Type ≥III: 59 (29%)	124M, 78F 202 C
Placebo-Controlled, Phase III							
PCT 302/99 Jun 1999 to Jan 2000 Final	Denmark, Norway (Denmark)	Patients with mild, moderate, or severe lesions in any location Unlimited number of lesions per patient	Phase III, stratified, randomized, stratified, double- blind, placebo- controlled	Tradename 168 mg/g or placebo for 3 h before illumination with a light dose of 75 J/cm ² (wavelength 570 to 670 nm)	1 or 2 applications: Single treatment for lesions on face and scalp Second treatment after 1 week for lesions at other locations	38 treated 39 included in safety population 43-87 (68) Type I: 10 (26%) Type II: 27 (69%) Type ≥III: 2 (5%)	25 M, 14F 39 C

Study Number Start Date/ End Date Report Status	Country/ Coordinating Investigator	Population Studied	Design Type of Control Blind	Dose(s) and Frequency of Dosing	Treatment Duration (does not include follow-up period)	No. Pts. Treated Age range (mean) (years) Fitzpatrick skin type	Sex; Race (Caucasian, Non-Caucasian Unknown)
PCT 305/99 Mar 2000 to Dec 2000 Final	Australia	Patients with mild or moderate AK lesions of the face or scalp Unlimited number of lesions per patient	Phase III, randomized, double-blind, comparative vs cryotherapy and placebo	Tradename 168 mg/g or placebo for 3 h followed by illumination with a light dose of 75 J/cm ² (wavelength 570 to 670 nm) Cryotherapy: liquid nitrogen spray; 1 freeze-thaw cycle	Two treatments of 3 hours each; 7 days apart	200 33-89 (64) Type I: 74 (37%) Type II: 85 (43%) Type ≥III: 41 (21%)	119 M, 81 F 200 C
PCT 306/99 Jun 2000 to Feb 2001 Final	US	Patients with mild or moderate AK lesions of face or scalp 4 to 10 lesions per patient	Phase III, randomized, double- blind, placebo- controlled	Tradename 168 mg/g or placebo for 3 h followed by illumination with a light dose of 75 J/cm ² (wavelength 570 to 670 nm)	Two treatments of 3 hours each; 7 days apart	80 31-84 (65) Type I: 20 (25%) Type II: 35 (44%) Type ≥III: 25 (31%)	70 M, 10 F 80 C

C. Post-Marketing

As previously mentioned, On June 26, 2002 the Agency was notified that Tradename® Cream has been approved for sale in both Sweden and Norway. An exact date of approval was not provided; however according to the original submission, Tradename® Cream had not been marketed as of September 2001. According to a submission received from the Sponsor on 06-28-02, to date, no AEs from these countries have been reported to PhotoCure ASA.

D. Literature Review

The literature submitted was not reviewed in depth. The articles submitted did not appear to relate to safety data in humans.

V. Clinical Review Methods

A. How the Review Was Conducted

For the NDA, two Phase 3 clinical trials (PC T305/99 and Study PC T306/99) are considered pivotal trials to support efficacy and safety at the proposed regimen of two treatment session 7 days apart and two trials are considered supportive (PC T301 and PC T 302). None of the Phase 3 trials were identical in that dosing regimen and study designs were different. Studies 302/99 and 306/99 were placebo-controlled and consisted of two PDT-treatment sessions 7 days apart for lesions of the scalp and face; however, Study 305/99 also included a cryotherapy comparative study arm. In Studies PC T301 and PC T 302, lesions located on the face and scalp were treated only once. Study PC T301/99 was placebo controlled; however, PC T301/99 was a comparative study that did not include a placebo control study arm.

One placebo-controlled Phase 3 study, PC T306/99, and the dermal safety studies were performed in the United States. The remainder of the clinical development program that included one Phase 2 study and three other Phase 3 studies were conducted in Europe (202/98, 301/99, 302/99) and Australia (305/99).

B. Overview of Materials Consulted in Review

Materials reviewed include:

NDA 21-415 Vol. 1.1, 1.21 – 1.40, User Manual PhotoCure™ Halogen PDT Lamp CureLight BroadBand CE 0470 (Version 2.1), Medical Officer's Review of NDA 20-965, and 3 Microbiology Consults (one to HFD 520 and two to HFD 580).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

No DSI audits were performed.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

According to the submission, except the initial compassionate use Study 001/97 (Vol. 1.37, pg. 19), all studies were conducted in accordance with Good Clinical Practice and in compliance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (CPMP/ICH//135/95). Foreign studies were conducted in accordance with the ethical principles of the Declaration of Helsinki. However to this reviewer, of concern are the following: the role of the study nurse in the U.S. study, safety monitoring may have not been optimal and lack of instructions from the Sponsor to investigators regarding disinfection/sterilization procedures for between patient use of the device.

E. Evaluation of Financial Disclosure

The Sponsor submitted the following statement that appears to meet the requirements for adequate financial disclosure:

"I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In two Phase 3 clinical trials (PC T306/99 and PC T305/99), two photodynamic therapy sessions conducted with Tradename Cream has shown superiority over placebo cream in treatment of actinic keratoses (p-value <0.001) at the 3-month efficacy endpoint. The two-stage process involves the following: (1) superficial preparation of the lesions followed by application of Tradename® 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 and total light dose of 75 J/cm² using the CureLight lamp. The entire two-stage process is repeated twice 7 days apart.

Efficacy of only one-treatment session for AK lesions located on the face and scalp was not substantiated by a second placebo-controlled trial. Additionally, the sample size was small with only 37 (19 active and 18 placebo) patients evaluated for safety and efficacy and blinding was problematic during a portion of the trial in that the caps on study medication tubes were color coded by content (active vs. placebo). The remedy (independent review of photographs) to

determine whether bias had been introduced indicated that bias had been introduced. Excellent response rates for clinical vs. photographic evaluations of 38% vs. 38% and 11% vs. 28%, active and placebo; respectively were reported. The Sponsor's rationale for discrepancies between the two evaluations seemed logical in that thin AK lesions are better felt than seen and the results were influenced by the skewed distribution of thin and moderately thick lesions; however, photographic evaluation data were not submitted to the NDA.

Reviewer's comments:

In both studies (PC T306 and PC T305) the active and vehicle were similar in appearance; however, adequate measures were not taken to minimize bias as per CFR §314.126 (5). Although blinding is problematic due to the phototoxic nature of the active, optimal blinding is possible if a qualified investigator not involved with lesion preparation, illumination, and safety evaluation conducted the efficacy evaluation.

In Study PC T306 (conducted in the U.S.) the Sponsor attempted to improve blinding (in that the investigator who prepared the lesion did not administer the light treatment and record AEs). However, it is the opinion of this reviewer that blinding method employed by the Sponsor may have compromised safety in the U.S. study in that it is uncertain whether qualified investigators performed the safety evaluation for the U.S. study. In Study PC T305 (conducted in Australia), the same investigator conducted lesion preparation, illumination, safety evaluation, and efficacy evaluation.

B. General Approach to Review of the Efficacy of the Drug

Data from Phase 3 studies PC T 306/99 and PC T 306/99 were reviewed to support the safety and efficacy of Photodynamic Therapy With Tradename®160 mg/g Cream in the treatment of nonhyperkeratotic actinic keratosis located on the face and scalp.

Phase 3 studies PC T302/99 and PC T301/99 are considered supportive in that: 1) a different treatment regimen was used (e.g., one treatment session for actinic keratosis lesions located on the face and scalp), the study was conducted in only 39 patients (20 active and 19 vehicle), and 3) blinding was problematic. Additionally, there is difficulty in assessing a reliable estimate of the treatment effect for the one treatment session regimen, as no placebo arm was included in Study PC T301/99. The Sponsor was advised by the Division at the EP-2 meeting held on June 22, 2000 that instructions on how to decide whether one or two treatment sessions are to be administered was needed; however, no instructions were provided.

C. Detailed Review of Trials by Indication

Indication #1 Treatment of Actinic Keratoses Sponsor's Protocol # PC T 306/99.

Title: "A Multicenter, Phase III, Double Blind Study of Photodynamic Therapy With Tradename®160 mg/g Cream Or Placebo Cream in Patients With Actinic Keratosis."
(Study Dates June 10, 2000 to February 2, 2001)

Protocol

Objective/Rationale

The primary objective was to compare the rate of patient response graded as complete response, defined as complete disappearance of the lesion, after photodynamic therapy using Tradename®

cream to that of photodynamic therapy using placebo in the treatment of actinic keratosis (AK) lesions.

Overall Design

This is a multicenter, randomized, double blind, placebo-controlled, parallel group study conducted in the United States. Randomization was stratified by center.

Population, procedures

Diagnosis and Significant Inclusion/Exclusion Criteria

Males or females above 18 years of age with a clinical diagnosis of 4-10 previously untreated, grade 1 or 2 AK lesions on the face and scalp, with diameters of 3 mm or more were suitable for entry. The lesions were graded according to the following:

- Grade 1 (mild) – slightly palpable AK, better felt than seen
- Grade 2 (moderate) – moderately thick AK, easily felt and seen
- Grade 3 (severe): were thick and/or obvious AK

This grading (mild and moderate) corresponds to the grading into thin and moderate, which appears in the Sponsor's text and tables of the submission.

Patients fulfilling any of the following criteria were ineligible for inclusion:

- Patients with porphyria.
- Patients immunosuppressed for either idiopathic, disease specific or therapeutic reasons.
- Use of topical corticosteroids on lesional areas within 2 weeks of PDT.
- Use of topical retinoids, alpha-hydroxy acids, systemic retinoids, chemotherapy or immunotherapy within 4 weeks of PDT.
- Pigmented AK lesion(s).
- Known allergy to Tradename[®], a similar PDT compound or excipients of the cream.
- Patients with history of hypersensitivity to nut products.
- Pregnant or breast-feeding: All women of child-bearing potential had to use adequate contraception (oral contraceptives, barrier contraceptive methods, or intrauterine device) during the treatment period and one month thereafter. In addition, a negative pregnancy test had to be obtained prior to treatment.

Study Plan

Two treatment sessions were scheduled 7 days apart and efficacy was assessed 3 months after the last treatment session. There was a total of five scheduled visits and the total study duration was at least three months. The visits were scheduled as follows:

- 1) Screening Visit (comprising a run-in period of up to two weeks),
- 2) Treatment Visit 1 (within 14 days from screening),
- 3) Treatment Visit 2 (7 days after first treatment),
- 4) Follow-up Visit (2 weeks after the last treatment for assessment of any adverse events and medication)
- 5) Follow-up Visit at 3 months after the last treatment for response assessment.

Reviewer's comments: *Three-month follow-up is inadequate for incidence of recurrence and long term safety assessment. At the EP-2 meeting, the Sponsor was strongly encouraged to modify the proposed Phase 3 protocol to permit assessment of recurrence in treated patients after 12 months. At that time it was not clear whether the long-term efficacy results from the Phase 2 study already completed by the Sponsor could be extrapolated to the Phase 3 studies if*

there are substantial differences in the study design between the Phase 2 and Phase 3 studies. However, the Phase 3 studies were not modified for assessment of recurrence as recommended.

Additionally, a cumulative contact sensitization study had not been performed prior to the pre-NDA meeting of May 2, 2001 and the contact sensitization potential of methyl-aminolevulinic acid HCl was not known. Unlike Levulan Kerastick (aminolevulinic acid HCl), the methyl-aminolevulinic acid HCl formulation (Tradename Cream) appears to be a potent sensitizer (Discussion in Dermal Safety Studies Section). Since new and recurrent lesions are expected in this patient population, re-treatment data are needed for Tradename® Cream.

Based on the Sponsor's conclusion of possible sensitization of 3 out of 25 subjects studied, up to 30% (upper 95% confidence interval) contact sensitization incidence rate is projected based on the result of Study PC T108/01. The actual number of patients displaying evidence of contact sensitization in Study PC T108/01 may be as high as 8 out of 25 (32%) which according to the Stat reviewer, is a rate of 53.5% upper 95% confidence limit (based on Clopper-Pearson). The study was conducted in 25 subjects and stopped with only a 9-day induction period (instead of the customary 21-day induction period) and the rate may have been even higher than 54% had the study continued for the customary 21 days.

One biopsy was to be performed if one or more lesion(s) did not respond to treatment. If the patient refused possible biopsy, he or she was still included in the study provided that the inclusion criteria and none of the exclusion criteria were fulfilled.

Lesion mapping was performed by numbering the lesions per subject from one to ten in the case report form (CRF). To assess the locations, the lesions were drawn and numbered on the CRF body chart page. Overview photographs and a photograph of each lesion were taken to establish location of the treated lesions. The number assigned to each lesion remained the same throughout the study to aid in efficacy evaluation. Photographs were taken of the lesions included in the study within 14 days before treatment, and at the 3-month visit.

Reviewer's comments: *Lesion mapping was not particularly good in that anatomical landmarks were not used; however from review of a limited number of CRFs (facial diagram drawing, before and after photographs), the same sites appeared to have been assessed for efficacy. It was noted by this reviewer that the informed consent form (Vol. 1.22, pg. 262) states that non-identifying photographs of the affected areas of your face and scalp during the Visit 1; however, the full-face photographs have no blocking of patient identity.*

Randomization

Patients were allocated numbers consecutively either to PDT with Tradename® and placebo cream from an electronic randomization list.

Blinding

The Tradename® and placebo creams were of identical appearance. Patients receiving active treatment were expected to have a higher rate of local phototoxic reactions during illumination than patients given placebo; therefore, a study nurse who was not involved in the lesion evaluation handled all procedures related to administration of light, including recording of local

adverse events. Consequently, investigator, patients and the sponsor were blinded to the identity of the test medication.

Reviewer's comments:

Blinding was problematic due to the nature of the active treatment. To optimize blinding, two investigators (i.e., minimally two physicians) should have participated at each study site (one to evaluate efficacy and one to evaluate safety) as per advice given to the Sponsor by the Division at the pre-IND (EP-2, pg. 4) meeting held on June 22, 2000.

Treatments Administered

Tradename[®] cream 160 mg/g or placebo cream was to applied for three hours up to 3½ hours being acceptable, followed by illumination using non-coherent light with a fluency of 75 J/cm² and fluency rate of 50-200 mW/cm². To ensure that all centers were given similar instructions, the entire treatment procedure (lesion preparation, cream application and removal and the illumination procedure) was demonstrated to the investigators before patient enrollment and all centers were provided with a video showing the treatment procedure. The specifics of treatment administration are described below.

Reviewer comments:

According to Submission NC received 12-14-01 (pg. 2) the videotape was used as an aid and not as the educational tool for investigators.

The Sponsor found it necessary to demonstrate the procedure of both lesion preparation and illumination to the investigators. According to the Sponsor's response received on 04-29-02, two U.S. principal investigator's and study nurses visited the _____ and the treatment procedure was demonstrated on a series of patients May 15, 2000. Subsequently, the procedure was demonstrated at an investigator meeting held in Norfolk, VA on June 17, 2000. Two other investigators were visited for training of treatment procedures on September 1 and 28, 2000.

Prior to approval as part of labeling, visual instructional material (e.g., video, CD, etc.) should be developed and distributed with the drug product to ensure optimal safety and efficacy with use of the drug-device. The material should not be promotional in nature and submitted to the Agency for approval prior to distribution. The instructional material should include (but not limited to) dosage and administration procedures, _____ and adequate procedures to prevent cross contamination with between patient use of the device.

Preparation of the lesion

Prior to administration of Tradename[®] or placebo cream, the lesion was prepared in order to facilitate access of Tradename[®] and light to all parts of the lesion. Preparation of the lesion, when applicable, was performed before each treatment. The extent of preparation depended on the nature of the lesion, scales and crusts were to be removed to ensure that illumination was not blocked. Scales and crusts were removed by a small dermal curette and the surface of the lesion was scraped gently in order to roughen the surface. The preparation was not intended to be

curative and the procedure was performed in both treatment groups (active and placebo). According to the Sponsor, if the preparation procedure had any effect in itself this should be reflected in the response rates of both treatment groups. The difference between the groups should be attributable to the type of cream used.

Reviewer's comments: *Open wounds may be produced with use of the dermal curette at the first treatment session and perhaps even a greater potential for open wounds at the second treatment session due to epidermal damage sustained after the first treatment.*

Cream application

A thick layer of study cream was applied directly to the lesion and on 5 mm of surrounding tissue. The amount of cream that was used depended on the size of the lesion. For all lesions, a thick (approximately 1 mm) layer of cream was applied to cover the lesion completely. An occlusive dressing (Tegaderm[®], 3M) was used. The center cut-out plate of the Tegaderm[®] was removed and the paper liner from the paper framed dressing peeled off. Tegaderm[®] was to cover the area of study cream application. The cream was spread over the entire lesion and to about 5 mm of surrounding tissue, either with a spatula prior to occlusion or by pressing the dressing down over the cream after the cream had been applied to the lesion. The dressing edges should be smoothed down to ensure that the dressing was fixed, then the paper frame of the Tegaderm[®] was removed.

When the cream had been applied for at least 3 hours, the occlusive dressing was removed and the study cream was gently wiped off with non-sterile gauze dipped in a non-sterile saline solution (0.9% sodium chloride).

Reviewer's comments:

- *The amount of cream applied should have been documented and presented in the NDA.*
- *The Sponsor should justify the use of non-sterile gauze and non-sterile saline solution on areas where there could be open wounds. The protocol change is not known to have been submitted to the IND.*

The illumination procedure commenced after removal of the cream.

- Each center was provided with **two lamps**, so that two widely separated lesions or two fields of illumination covering multiple lesions could be treated simultaneously.
- For additional fields, the illumination procedure had to be repeated. In those cases, the study cream was to remain occluded until the illumination procedure began.
- A total application time of 3 1/2 hours was acceptable.
- No special precautions were necessary in the 3 hours period from cream application to removal, or after treatment.

Reviewer's comments:

- *The Sponsor was advised to plan a strategy for patients who have many lesions, perhaps staggering the application of the cream to various lesions to insure that no lesion is treated outside the time window of 3 1/2 hours. No such strategy was noted in the protocol. The Sponsor was advised the Pre-IND/EP-2 meeting significant delay in irradiation of the last lesions of patients could be encountered in those with 10 or more lesions. For example, a*

patient with 10 lesions could require at least 50 minutes of irradiation, which added with delays of setting up the light session from one lesion to the next would add significant delays in irradiation of the last lesions of patients.

- *Tegaderm is not opaque; however, no special precautions were necessary in the 3 hours period from cream application to removal, or after treatment.*

Illumination procedure

Illumination was performed after removal of the dressing and the cream from the skin. The skin area that was covered with cream was illuminated with red light (570-670 nm) with a fluency of 75 J/cm². The illumination procedure was demonstrated to the trial personnel, and described in the User Manual for the PhotoCure lamp. For additional fields, the illumination procedure had to be repeated. The average time needed for a light dose of 75 J/cm² is about 10 minutes, depending on the size of the field of illumination. The PDT procedure was repeated seven days after the first treatment session.

Reviewer comments:

- *Data should have been collected regarding total illumination time per patient, the number of lamps used, and the number of treatment fields per patient. Safety and efficacy of overlapping treatment fields was not addressed. According to the Sponsor, two lamps were used for patients with multiple or widely separated lesions to keep the treatment time within reasonable limit.*
- *According to the Sponsor there could theoretically be 10 treatment fields; therefore in patients with multiple, widely separated lesions, application time could far exceed 3 ½ hours even with use of two lamps. The Sponsor stated that when two lamps were used, up to 6 treatment fields could be treated within a maximum of 45 minutes.*
- *There were no restrictions on the number of treatment fields in the U.S. study (Study PC T 306/99) as in an Austrian study (PC T 305/99). A rationale for restricting treatment to no more than 6 circular fields with maximum diameter of 5.5 cm (Vol. 1.25, pg. 16) in Study PC T 305/99 was not provided.*

When treating lesions close to the eye, the patient wore eyeshields that fitted tightly to the skin to protect the eyes from the intense light. The Sponsor provided the eyeshields (eyeshield). The study personnel were recommended to use ordinary sunglasses during illumination due to the intense light. UV light is not emitted from the light source.

Identity of Investigational Products

Tradename[®] cream (methyl 5-aminolevulinate hydrochloride) 168 mg/g

- The strength is given as the concentration of the active entity, methyl 5-aminolevulininate, which is present as the hydrochloride.
- Supplied in 2 g collapsible aluminum tubes, which should be stored in refrigerator (2-8°C) at the hospital pharmacy, or at the study site in case of no available pharmaceutical service.
- Batch number: 0080S
- Contract manufacturer: Penn Pharmaceuticals Ltd
Tredegar
Gwent NP2 3AA, United Kingdom

Reviewer's comment: *According to the oral communications with the reviewing Chemist, the active drug is stable at room temperature for approximately — however, the instability does not pose a safety hazard but would affect efficacy of the product.*

Placebo cream

- The excipients were identical to those of the vehicle of the active cream, except for addition of Hard Paraffin as a stiffening agent and Yellow Iron Oxide E172 for color matching of the active cream.
- Supplied in 2 g collapsible aluminum tubes, which should be stored in refrigerator (2-8°C) at the hospital pharmacy, or at the study site, in case of no available pharmaceutical service.
- Batch number: 0236T
- Contract manufacturer: Penn Pharmaceuticals Ltd
Tredegar
Gwent NP2 3AA, United Kingdom

Light source

- The lamp emitting red light uses a 150 W halogen lamp, which is collimated by means of an elliptical mirror and focused by a lens through various filters. This produces the appropriate wavelength band (570-670 nm). The lamp illuminates a circular area, 30-55 mm in diameter as required at its end plane, and is cooled by a fan situated in the rear end. The homogenous light field gives an intensity of 50-200 mW/cm² – depending of diameter used, which is monitored by a detector placed on the skin and presented at the panel of the control unit. The lamp was supplied by PhotoCure ASA

Reviewer's comments:

Possible cross-contamination between patients with use of the device is an unresolved safety issue. The Division of Anti-Infective Drug Products was consulted regarding the Sponsor's plan for between patient disinfecting of the light measuring diode. Lesion preparation might produce an open wound and some bleeding since lesion preparation consists of debriding with a small dermal curette to remove scales, crusts, and to roughen the surface.

A light measuring diode device is being used for calibration prior to illumination with PhotoCure Halogen PDT Lamp for treatment of actinic keratosis with Tradename Cream. According to the User Manual (pg. 11), calibration should be performed with the light measuring diode placed at the lesion surface prior to illumination. The Sponsor's plan (User Manual, Section 8, pg. 15) for between patient disinfecting of the light measuring diode is not detailed; however, wiping with 70% isopropyl alcohol is implied.

According to the FDA Microbiology Reviewer, the method of diode sterilization is unsatisfactory and that both the instructions and method of disinfecting the light measuring diode are inadequate. Additionally, according to the Sponsor in response to a query received May 24, 2002 (via fax), the horseshoe-positioning device could also come in contact with an open wound. On May 28, 2002, the Division advised the Sponsor's U.S. Agent that the sterilization/disinfecting procedures are inadequate and this safety issue has a significant effect on approval of the drug-device combination. Additional review by CDRH with further discussion/consultation with the Division is pending at the time of this writing.

Efficacy and Safety Variables

The investigator performed baseline evaluation of the lesions. Treatment response was documented clinically through visual evaluation and palpation as well as cosmetically compared with baseline. All lesions treated in the study were to be photographed before and after treatment.

A follow-up visit to evaluate safety was performed two weeks after last treatment. Response evaluation was performed three months after last treatment. An extra visit might be performed if AEs or any other events warranted a visit to the clinic before three months.

The following assessments were performed during the follow-up evaluation 3 months after the last PDT as follows:

- Lesion response evaluation, including photography
 - Overall cosmetic evaluation
 - Patient preference
 - Histologic assessment of biopsy from one lesion per patient with treatment failure, provided patient consent
- AEs

Lesion response

The primary objective of the study was to determine whether the lesions had disappeared completely or not three months after treatment. The treatment response was documented clinically by evaluating the lesion both visually and by palpation. The investigator classified the response of each lesion as either:

- Complete response (CR) - complete disappearance of the lesion *or*
- Non-complete response (non-CR) – non-complete disappearance of the lesion.

Cosmetic outcome

The investigator and patient assessed the overall cosmetic outcome in patients with complete patient response (i.e. 100% of lesions in complete response).

Overall cosmetic outcome was assessed with regards to occurrence of the following signs or symptoms; scarring, atrophy, induration, redness or change in pigmentation. The cosmetic outcome was to be graded as:

Excellent	No scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared to adjacent skin.
Good	No scarring, atrophy or induration but moderate redness or change in pigmentation compared to adjacent skin.
Fair	Slight to moderate occurrence of scarring, atrophy or induration.
Poor	Extensive occurrence of scarring, atrophy or induration.

Reviewer comments: *Cosmetic outcome scale actually describes adverse events and should be included in the local AE listing and not listed separately and include both results from non-complete responders as well as complete responders.*

Histology

If consent was given, a 2-mm punch biopsy was taken from one randomly selected lesion with treatment failure in order to verify the AK diagnosis. The histological examination was

performed by the site's designated dermatopathologist. For those lesions that had a biopsy taken, the lesion number and the diagnosis from the histological examination was recorded in the CRF.

Safety

No systemic laboratory monitoring was conducted in this study. Safety was assessed in terms of AEs. Local phototoxicity was to be reported as an AE by the study nurse. Local skin reactions/phototoxicity were assessed during and after cream application and illumination. All AEs (local or systemic) were to be reported in the patient CRFs provided, but also in the patient records. All AEs were followed up until resolved or as clinically required.

Eyeshields (eyeshields) provided by the Sponsor were to be worn by patients when treating close to the eye. UV light is not emitted from the light source; however, due to the intensity of the light, use of ordinary sunglasses by study personnel was recommended.

Reviewer comments: *The quality and quantity of safety database submitted with the NDA does not include enough information to allow for compete and thorough safety assessment at the proposed dosing regimen. New data submitted for the first time at NDA submission and new information resulting from queries made by the Division during NDA review has made it evident that additional safety data is needed in order to make an informed risk benefit assessment for review purposes. Detailed discussion is located in Integrated Review of Safety. The following issues were addressed by the Division and are of concern:*

- *The Sponsor was advised that assessment of safety should include changes in laboratory parameters and if not included an adequate rationale for excluding this data should be presented by the Sponsor.*

A rationale for not assessing changes in systemic laboratory monitoring was not provided in the NDA; however, according to the Sponsor (Vol. 1.22, pg. 20), pre-clinical studies suggest negligible systemic absorption of radiolabelled methyl 5-aminolevulinate. The Sponsor did submit systemic laboratory data from 359 patients in Studies 202/98, 303/98, 204/98, and 205/98. These data were not obtained from patients treated at the proposed dosing regimen of two treatment sessions 7 days apart (see discussion under Adequacy of Safety Testing).

A possible liver toxicity signal was detected in the repeat dose data in the minipig study (e.g., slight increase in ALT); therefore, systemic laboratory monitoring data in humans for the two-treatment regimen exposure are needed. According to the Pharm/Tox reviewer, a repeat dose minipig study report requested at the end of phase 2 meeting to support the Sponsor's phase 3 clinical trials was submitted for the first time for the review with the NDA.

- *Possible cross-contamination between patients with use of the device is an unresolved safety issue.*
- *Adverse events should have been presented separately to assess drug effect alone from PDT for each of three time periods (during drug application, illumination, and post-treatment) as to the type and quantity of the adverse event. AEs resulting from the curettage procedure should have assessed separately.*
- *According to a response to query from the Sponsor received 04-29-02, if the study nurse felt that an adverse event required a physician's attention then the sub-investigator would get involved. Study nurses applied light illumination, monitored local adverse events, and did*

the safety evaluation 2-weeks after the second PDT treatment session. Additionally, a communication received July 24, 2002 indicates that the study nurse recorded both local and systemic AEs before and after each treatment session, at the 2-week post-treatment follow-up and at the 3-month efficacy study endpoint. The Sponsor did not indicate that these data obtained by or were reviewed by a qualified investigator.

An investigator "licensed to practice medicine" in the locale in which the study is conducted should be in charge of monitoring local and systemic safety. Ideally, two qualified investigators were needed at each center (a blinded investigator to assess efficacy and an unblinded investigator to assess safety).

Evaluability criteria

Primary Efficacy Variables

The primary efficacy variable was the percentage of patients in whom 100% of lesions had responded completely three months after treatment.

Primary efficacy

The primary efficacy variable was patient complete response based on lesion assessments performed 3 months after last PDT. Patient complete response was defined as 100% of the lesions within the patient showing complete response three months after last PDT.

Changes in the Conduct of the Study

Amendments to the protocol and Notes to the file

The revised and amended version of the study protocol, dated April 3, 2000, is the only version that has been submitted to IRBs and investigators, as described in "Note to the file", dated April 27, 2000. There were four amendments to this protocol, dated May 8, 2000, May 25, 2000, July 17, 2000 and August 22, 2000, respectively.

In **Amendment 1** the exclusion criterion regarding fertile women was changed to accept barrier methods in addition to oral contraceptives and intrauterine devices. In addition the description of the randomization procedure and the instructions for the PDT procedure were clarified.

In **Amendment 2** the definitions used to categorize AK lesions into grade 1 and 2, which had been incorrectly described in the study protocol, were corrected. This amendment was dated May 25, 2000 that was prior to the beginning of the study on June 10, 2000. The original protocol described Grade 2 lesions as well developed easily palpated to are easily seen and felt. Since the amendment was in effect prior to the start of the trial there would not appear to have an effect on the study endpoints except that lesions that thin lesions included provided a lower efficacy hurdle than thicker lesions would have provided.

Amendment 3 introduced a histological assessment of biopsies from a randomly selected sample of lesions with treatment failure in order to increase the certainty of the type of lesions treated. Patients with one or more lesion(s) in non-complete response had, if they agreed and signed a revised consent form, a biopsy taken. In case of multiple lesions in non-complete response, the lesion from which the biopsy was to be taken was randomly assigned. The exclusion criterion regarding hypersensitivity to nut products or other known protein antigens was changed to

comprise hypersensitivity to nut products only, which covers peanut and refined almond oils, which are the two excipients in the cream that may contain traces of allergens.

In addition, clarifications were made to the sections on lesion mapping, lesion preparation, dosage and administration of study cream, concomitant medication and procedures for the clinical response evaluation. These items were not adequately described in the original protocol and previous amendments.

Amendment 4 documented the inclusion of a fifth study center due to slow patient enrolment in the study.

Reviewer comments:

No protocol amendments are known to have been submitted to the Agency for the following:

- *The study nurse conducted the safety evaluations.*
- *In case of medical treatment of an adverse event, a sub-investigator was called upon (at the discretion of the study nurse) to treat the AE.*
- *The use of non-sterile gauze and non-sterile saline solution on open wound areas.*
- *Use of local anesthetics under special circumstances at patient request.*

Statistical Considerations (See Statistical Review)

Changes in the statistical analysis plan

The primary analysis was performed using the Cochran-Mantel-Haenszel Chi-square test (CMH test) with a significance level of 5%, instead of a plain chi-square test as described in the study protocol because, according to the Sponsor, the CMH test allows an adjustment for centers

No confidence intervals were calculated for the patient's individual mean weighted response rate weighted by number of lesions per patient.

Safety

The reported adverse events (including local reactions) were coded according to WHO terminology. The number and percentages of subjects with at least one adverse event were tabulated. Occurrence of particular adverse events, by body system and preferred WHO term, and their severity and relationship were summarized using number and percentages of patients. The local phototoxicity events were defined as all events coded under the WHO System organ Class "Skin and appendages disorders".

Study Results PC T306/99

A total of 80 patients were enrolled, randomized and treated at five sites located in the United States. Of these, 42 patients were treated with Tradename®-PDT and 38 patients were treated with placebo-PDT. The principal investigator, the investigator numbers, and the number of patients enrolled at each site follows in Table 3.

Table 3: Principal Investigator, The Investigator Numbers, and Number of Patients Enrolled at Each Site

Center, Investigator Name, Affiliation, and Location	Site #	Investigator No.	No. of Patients Enrolled
D. M. Pariser, MD Virginia Clinical Research, Inc. Norfolk, VA	1	30601	18
N. J. Lowe, MD Clinical Research Specialists, Inc. Santa Monica, CA	2	30602	24
A. W. Lucky, MD Dermatology Research Associates, Inc. Cincinnati, OH	3	30603	7
D. M. Stewart, MD Midwest Cutaneous Research Clinton Township, MI	4	30604	19
M. Jarrett, MD DermResearch, Inc. Austin, TX	5	30605	12

Demographics, Evaluability

Number of subjects (total and for each treatment):

	Tradename [®] cream	Placebo	Total
No. planned	40	40	80
No. randomised and treated	42	38	80
Males/Females	36/6	34/4	70/10
Mean age (range)	64 (31-84)	67 (39-84)	65 (31-84)
No. analysed for efficacy (ITT)	42	38	80
No. analysed for efficacy (PP)	39	38	77
No. analysed for safety	42	38	80

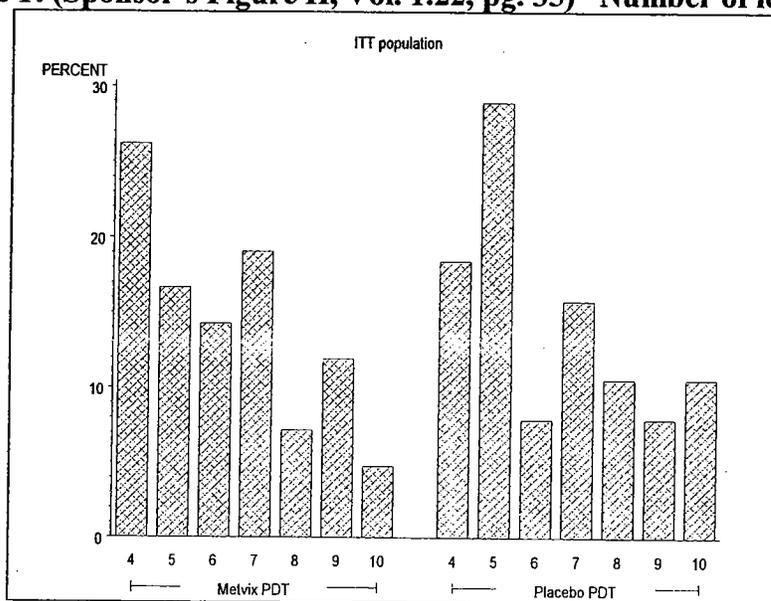
All patients were of Caucasian origin with Skin-Phototypes as follows: I in 25%, II in 44%, III in 24%, IV in 6%, and V in 1%. No reports of previous diseases were collected in the study. The most common concurrent diseases other than AK were disorders of the cardiovascular system (36% in the Tradename[®] PDT group and 45% in the placebo PDT group), endocrine and metabolic disorders (26% vs. 29%), and musculoskeletal disorders (24% vs. 18%). Essential hypertension and hypercholesterolemia were the most common diagnoses, reported by 23 and 22 patients, respectively.

Reviewer comments: *The Sponsor did not provide statistical comparison for baseline and demographic variables as requested at the Pre-NDA meeting minutes. According to the Division's Statistician, baseline characteristics were similar at baseline between active and placebo groups.*

Two patients in the Tradename[®] PDT group discontinued the study prematurely, both before the second PDT. One patient (No. 2003) discontinued due to an adverse event during the first illumination, and one patient (No. 2008) was lost to follow-up. One patient classified as a protocol deviator, (No. 4010) did not undergo the second treatment due to adverse event from the first treatment.

Baseline lesion description and location follows:

Figure 1: (Sponsor's Figure II, Vol. 1.22, pg. 35) Number of lesions per patient



A total of 502 lesions were included in the study, 260 lesions treated with Tradename[®] PDT and 242 lesions treated with placebo PDT. The number of lesions per patient ranged between 4 and 10. Forty-five percent of the patients had 4-5 lesions, 29% had 6-7 lesions and 26% had 8-10 lesions.

Table 4 (Sponsor's Table V, Vol. 1.22, pg. 36): Lesion location and description.

Treatment	Description	Number of lesions		Lesion location			
				Face		Scalp	
		n	%	n	%	n	%
Tradename [®] PDT	Grade 1 (AK thin)	196	75	168	65	28	11
	Grade 2 (AK moderate)	64	25	58	22	6	2
	Total	260	100	226	87	34	13
Placebo PDT	Grade 1 (AK thin)	162	67	129	53	33	14
	Grade 2 (AK moderate)	80	33	75	31	5	2
	Total	242	100	204	84	38	16
Total	Grade 1 (AK thin)	358	71	297	59	61	12
	Grade 2 (AK moderate)	144	29	133	26	11	2
	Total	502	100	430	86	72	14

Data source: Table 10, Section 14.1.

Most lesions were located on the face (86%), while 14% were located on the scalp, with a similar distribution in the two treatment groups. Grade 1 (thin lesions) accounted for 71% and grade 2 (moderately thick lesions) for 29%. In the placebo PDT group, a higher percentage of moderately thick lesions were included (33%), compared with the Tradename[®] PDT group (25%).

The lesion diameter before treatment ranged from 3 to 35 mm with a mean value of 7.5 mm (the largest diameter was measured), Table 11. The mean lesion diameter per patient ranged between 3.3 and 16.0 mm with a mean value of 7.4 mm, Table 12.

Clinical symptoms before treatment were present in 8 patients (10%). Almost all symptoms were related to the skin, with pain skin as the most common symptom

Measurement of Treatment Compliance

Compliance was not considered to be a problem, as the treatment was given at two occasions by the investigator. The only measurements performed were checking lesion preparation, that treatment was given according to randomization, that the actual application time was three hours and that the light dose and the illumination time were correct.

Out of the 260 Tradename[®] treated lesions 240 (92%) were given two PDT treatments, while 20 lesions were given only one PDT and were classified as protocol violators. All 242 placebo treated lesions were given repeated PDT.

Application Time, Light Intensity, Light Dose, and Light Field Diameter

The application time ranged from 2h 10min to 4h 45min hours with a median value of 3h 9min. The illumination time ranged from 1min to 16min 20sec with a median value of 8min 20sec. The light intensity ranged from 78 to 200 mW/cm² with a median value of 159 W/cm². The light dose was pre-set to 75 J/cm² and not recorded in the CRF. The light field diameter ranged from 35 to 55 mm with a median of 40 mm.

Reviewer comment: *The PhotoCure Lamp unit automatically calculates the illumination time; using the intensity and the specified dose. According to the Sponsor, the illumination time is about 10 –15 minutes for each field. Application time greater than 3½ hours should have been considered a protocol violation. Efficacy and safety data for those patients with application times beyond 3½ hours should have been provided.*

Efficacy

Efficacy results: The Sponsor concluded that statistical analyses confirmed Tradename[®] PDT to be superior to placebo PDT. The patient complete response rate in the ITT population (i.e. percentage of patients with 100% of lesions in complete response) was 79% (33 of 42 patients; 95% CI 63%-90%) in the Tradename[®] PDT group and 21% (8 of 38 patients; 95% CI 10%-37%) in the placebo PDT group.

Table 5 (Sponsor’s Table VI, Vol. 1.22, pg. 39): Patient Complete Response (ITT)

Treatment	Number of patients		Response category			
			Non complete		Complete	
	n	%	n	%	n	%
Tradename [®] PDT	42	53	9	21	33	79
Placebo PDT	38	48	30	79	8	21
Total	80	100	39	49	41	51

The Division's statistical analysis results supports the Sponsor's conclusion that Tradename-PDT is statistically superior to placebo-PDT (<0.001). See the table that follows:

Table 6 (Modified FDA Statistical Table 3): Subjects with 100% of Lesions Cleared 3-Month Post-Treatment

STUDY 306	Tradename (n=42)	Placebo (n=38)		p-value ¹
ITT analysis n (%)	33 (79%)	8 (21%)		< 0.001
PP analysis n/N (%)	32/39 (82%)	8/38 (21%)		< 0.001
Source: Sponsor's NDA submission (pages 78-81, Volume 42; pages 87-88, Volume 45)				
¹ p-value is the comparison between Tradename and Placebo groups, and is based on Cochran-Mantel-Haenszel test adjusting for center.				

In the Tradename[®] PDT group, lesions on the face had a response rate of 86% (195 of 226 lesions), while lesions in the scalp had a response rate of 76% (26 of 34 lesions). Corresponding figures in the placebo PDT group were 36% (73 of 204 lesions) for face and 50% (19 of 38 lesions) for scalp.

Reviewer's Comments/Conclusions of Study Results

In Study PC T307/99, two treatment sessions were conducted 7 days apart with Tradename[®] 168 mg/g cream or vehicle cream applied for 3 hours before illumination in treatment of slightly palpable (better felt than seen) to easily felt and seen actinic keratoses located on the face or scalp. Eighty patients entered and were treated in the study, 42 with Tradename[®]-PDT and 38 with placebo-PDT. The primary variable was the patient complete response, i.e. percentage of patients with all lesions in complete response, assessed three months after the second PDT treatment. Cochran-Mantel-Haenszel test, Tradename[®] PDT demonstrated statistical superior (p-value <0.001) to placebo PDT in complete patient response in the ITT population.

Blinding was not optimal since the same investigator performed lesion preparation (removing crusts, etc.) prior to the second PDT treatment session also evaluated efficacy at the efficacy endpoint. Patients with AEs (e.g., crusting, blisters, and erythema) present at the second treatment session that could perhaps break the blind were imputed as failures; however, sensitivity analyses shows that overall Tradename-PDT is better than placebo-PDT.

Sponsor's Protocol PC T305/99 (conducted in Australia and not under the IND)

Trial Dates: March 8, 2000 (first pt. treated) December 5, 2000 (last follow-up pt.)

Title: "A Multicentre, Phase III, Randomized Study of Photodynamic Therapy (PDT) with Tradename[®] 160mg/g Cream in Comparison with Cryotherapy and PDT with Placebo Cream in Patients with Actinic Keratosis."

Objective Rationale

Sponsor's Stated Primary Objectives

- To compare the weighted patient response rates of Tradename[®] PDT and cryotherapy.
- To compare the weighted patient response rates of PDT using Tradename[®] and PDT using placebo cream

Secondary Objectives

- To compare lesion response, cosmetic outcome and tolerability (adverse events) in three patient groups.
- To compare the 100% patient response rates.

Design

This study was a randomized, comparative, parallel group multicenter study, comparing the efficacy and tolerability of PDT using Tradename® cream, conventional cryotherapy and PDT using placebo cream in the treatment of AK lesions. The study was open with regards to PDT vs. cryotherapy and double-blind with regards to Tradename® vs. placebo PDT.

Reviewer’s comments:

- *As noted on page 9 of the pre-NDA meeting minutes, the Protocol 306/99 was not a comparative study (Tradename vs. cryotherapy vs. placebo). Study 305/99 was ongoing prior to the EP-2 meeting between the Sponsor and the Division and no prior commitments were made for Protocol 305/99. Two pivotal studies with a cryotherapy arm would be needed to substantiate efficacy results; therefore, the cryotherapy study arm will not be review to assess clinical efficacy.*
- *Blinding was also problematic in this study in that the same investigator prepared the lesion, administered treatment, and provided efficacy evaluation*

Protocol Overview

Table 7: Summary of Differences Between Study 306/99 and Study 305/99

Location	306-99 (US)	305/99 (Australia)
No. of Study Arms Randomization	2 arm study (Active vs. Vehicle) (1: 1)	3 arm study (Active vs. Cryotherapy vs. Vehicle) (1:1:4)
No. of Lesions, size and location	4 – 10 previously untreated, grade 1 or 2 , diameters of 3 mm or more	Up to 10 lesions with more than 10 excluded, mild or moderate (equates to grade 1 or 2, respectively) on face/scalp*
Lesion exclusion	Not separately addressed	Lesion not suitable for cryotherapy
Number of Treatments	2 PDT sessions one week apart for face and scalp lesions	Same for PDT; however, cryotherapy was applied once
No. of circular fields and number of lamps	<ul style="list-style-type: none"> • No restriction on the number of fields stated in the protocol • Two lamps could be used 	<ul style="list-style-type: none"> • 6 circular fields maximum diameter 5.5 cm (vol. 1.25, pg. 16) • Not clear on the number of lamps used
Blinding	(vol. 1.22, pg. 20) <ul style="list-style-type: none"> • A study nurse who was not involved in the lesion evaluation handled all procedures related to administration of light, including recording of local adverse events. • Creams were identical in appearance and all patients were exposed to light. 	(vol. 1.25, pg. 20) <ul style="list-style-type: none"> • The study was blinded before treatment allocation, i.e. each patient was given a cream tube with either Tradename® or placebo cream (patients in the cryotherapy group were also given a tube of placebo cream) in order

		<p>to avoid bias before the randomization envelope was opened.</p> <ul style="list-style-type: none"> For the active and vehicle groups, creams were identical in appearance.
Safety	Follow-up with the study nurse to evaluate safety after the last treatment	Telephone contact 2 weeks after second treatment
Sponsor's Primary Efficacy Variable	The primary efficacy variable was the percentage of patients in whom 100% of lesions had responded completely three months after treatment	The primary efficacy variable was the patient's individual response rate weighted by number of lesions per patient

Amendments to the protocol

There were two amendments to the study protocol dated 20.01.00 and 06.06.00, respectively. The Amendments are as follows:

Amendment #1 (January 20, 2000)

The criteria regarding lesion size and number of lesions were changed. Lesions with largest diameter less than 5 mm were to be excluded and patients with more than 10 eligible lesions might be included, but the lesions should be distributed in a manner that allowed all eligible lesions to be treated using no more than 6 circular fields with maximum diameter 5.5 cm.

The cryotherapy procedure was also adjusted in order to reflect the standard treatment used by the investigators, i.e. only one freeze-thaw cycle was to be used. A secondary parameter to study patient satisfaction with the treatment was added. Patient satisfaction with PDT in relation to any previous treatment(s) was to be asked for in the PDT group.

Amendment #2 (June 6, 2000)

Amendment 2 involved changes to the definition of the primary endpoint, and the statistical methods used to analyze the primary endpoint. At the suggestion of the United States health authorities, the superiority hypothesis was to be tested on the results of the ITT population, whereas the non-inferiority hypothesis was to be tested on the results of the PP population, which was defined in this amendment.

The number of patients in whom 100% of the lesions responded completely after 3 months was added as a secondary parameter, because health authorities have requested to see this endpoint. The timelines were also extended to allow patient inclusion to continue through July 2000.

Population procedures

The study plan was similar to Study PC T 306/99 except as noted above. The study drug was the same.

Study Results

A total of 205 patients were planned, 204 patients were randomized, and 200 were treated at nine study centers in Australia. Eighty-eight (88) patients were randomized to the Tradename® cream/PDT arm, 89 were randomized to the cryotherapy arm, and 23 to the

placebo/PDT treatment arm. Table 8 lists the principal investigators, investigator number, and number of patients enrolled at each site.

Table 8: Center, Investigator, Location, and Total No. of Patients Treated

Center, Investigator Name, Affiliation, and Location	Site #	Investigator No.	Total No. of Patients Treated
Dr. Peter Foley Department of Dermatology St Vincent's Hospital Fitzroy Victoria 3065	Site # 001	30501	22
Dr. Michael Freeman Suite 5, AHC House 14 Carrara Street Benowa Queensland 4215	Site # 002	30502	40
Dr. Lynda Spellman The Belmont Specialist Clinic 1202 Creek Road Carina Queensland 4152	Site # 003	30503	28
Dr. Warren Weightman Dermatology Department The Queen Elizabeth Hospital Woodville Street Woodville Adelaide South Australia, 5000	Site # 004	30504	20
Dr. Cathy Reid Royal Adelaide Hospital North Terrace Adelaide South Australia, 5000	Site # 005	30505	12
Dr. Dedee Murrell Dept. of Dermatology St. George Hospital Belgrave Street Kogarah, New South Wales 2217	Site # 006	30506	20
Prof. Chris Anderson 1 st Floor, Suite 7, Goulburn Medical Centre Liverpool Hospital 45-47 Goulburn Street LIVERPOOL, New South Wales 2170	Site # 007	30507	18
Dr. Alan Watson Royal Newcastle Hospital Pacific Street NEWCASTLE NSW 2300	Site # 008	30508	11
Dr. Carl Vinciullo Dermatology Surgery & Laser Centre The Perth Surgicentre Suite 12, 38 Meadowvale Ave PO Box 8115 SOUTH PERTH WA 6151	Site # 009	30509	33

Demographics and Baseline Characteristics (Study PC T305)

	<u>Tradename® cream</u>	<u>Cryotherapy</u>	<u>Placebo</u>	<u>Total</u>
No. planned	95	95	15	205
No. randomised	91	90	23	204
No. treated	88	89	23	200
Males/Females	49/39	54/35	16/7	119/81
Mean age (range)	64 (33-86)	65 (38-86)	66 (49-89)	64 (33-89)
No. analysed for efficacy (ITT)	88	89	23	200
No. analysed for efficacy (PP)	77	86	19	182
No. analysed for safety	88	89	23	200
No. completed	87	87	23	197

Reviewer's comments:

As in Study PC T 306/99, the Sponsor did not perform statistical comparison for baseline and demographic variables as requested by the Division to ensure that efficacy results were not driven by baseline differentials between treatment.

Patient Disposition

According to the submission, there were 7 patients who discontinued from the study, 4 were randomized to the Tradename® PDT study arm and 3 to the cryotherapy study arm. Three patients in the Tradename arm discontinued prior to treatment and one in the cryotherapy arm.

Discontinuations from the study are as follows:

Prior to treatment:

- consent withdrawn (nos. 1021 & 6012)
- lost to follow-up (no. 3008)
- other (no. 1003)

After treatment:

- adverse event (no. 3014)
- lost to follow-up (nos. 3016 & 3026)

According to the submission (Vol. 1.25, pg. 34), 200 patients were included in the ITT and safety analyses excluding four patients who did not receive any treatment.

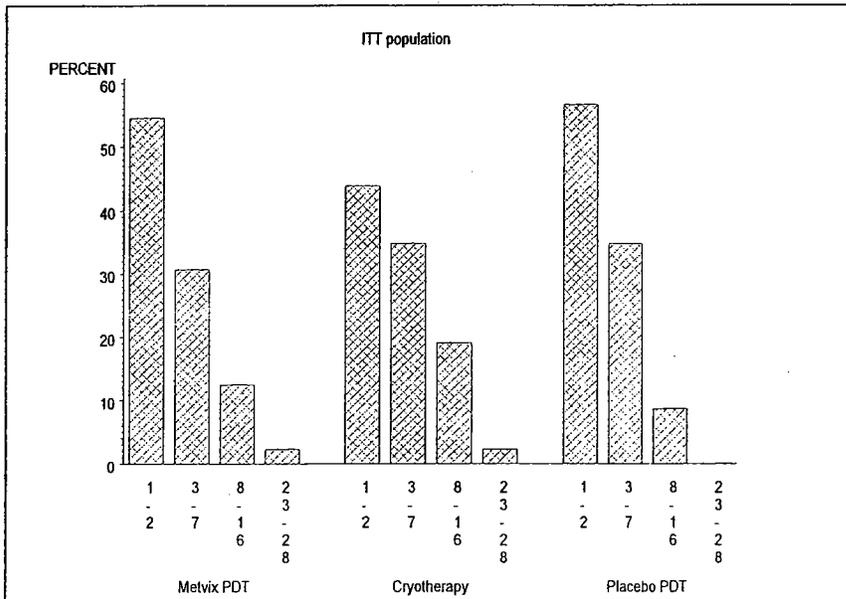
Reviewer's comments:

The intent-to-treat (ITT) population should include all patients who were randomized to treatment. According to Section 10.1 (Vol. 1.25, pg. 33), 204 patients were randomized; therefore, efficacy and safety analyses should include the actual number of patients who were randomized to treatment groups.

Protocol Deviations

Protocol deviations were as follows: 1) incorrect light intensity in 8 patients, 2) light dose in 5 patients, 3) incorrect number of treatments in 15 (13 active, 1 cryo, & 1 placebo), and 4) incorrect treatment arm (Pt. # 1001 was randomized to PDT received cryo, 5009 & 5012 randomized to cryo were given PDT placebo).

Figure 2 (Sponsor’s Figure III, Vol. 1.25, pg. 36): Number of lesions per patient



According to the Sponsor (Vol.1.25, pg. 16), the January 20, 2000 Amendment changed the criteria and lesions with largest diameter less than 5 mm were to be excluded and patients with more than 10 eligible lesions might be included. The lesions were to be distributed in a manner that allowed all eligible lesions to be treated using no more than 6 circular fields with maximum diameter 5.5 cm.

Reviewer comments: *The need to raise the upper limit of lesions for entry is perplexing since study results indicates that actually at baseline, 31% (34/111) of the enrolled patients had 4 to 10 lesions , 63% (70/111) of patients had less than 4 lesions, and only 6% (7/111) had more than 10 lesions present at baseline.. According to analysis by the Division’s Statistician, at baseline the number, size, and severity were comparable between the active and placebo study arms. Overall, the data do not suggest that the placebo group had more severe patients than the active.*

Sponsor’s complete response rate

Table 9 (Sponsor’s Table VI, Vol. 1.25, pg. 37.): Patient Complete Response

Treatment	Number of patients		Response category			
			Non complete		Complete	
	n	%	n	%	n	%
Tradename PDT	88	44	17	19	71	81
Cryotherapy	89	45	38	43	51	57
Placebo PDT	23	12	20	87	3	13
Total	200	100	75	38	125	63

Data Source: Table 24, Section 14.2.

The patient complete response rate was 81% in the Tradename[®] PDT group, 57% in the cryotherapy group and 13% in the placebo PDT group. The 95% confidence intervals ranged from 71% to 88% for Tradename[®] PDT, from 46% to 68% for cryotherapy and from 3 to 34% for placebo PDT.

Reviewer's comments:

As previously noted, efficacy data from the cryotherapy arm of the study will not be used to support approval of the NDA. Pivotal Study 306/99 did not have a cryotherapy study arm and due to the nature of the treatment, blinding was non-existent after randomization. Additionally, the mean freeze time was only 13 seconds. An investigator not involved with administering the therapies and safety evaluation would have been useful for an unbiased efficacy evaluation for all study arms.

**Table 10: (Modified Statistical Table 1.):
Percentage of Subjects with 100% of Lesions Cleared 3-Month Post-Treatment**

SUTDY 305	Tradename (n=88)	Placebo (n=23)	p-value ¹
ITT analysis n (%)	71 (81%)	3 (13%)	< 0.001
PP analysis n/N (%)	63/77 (82%)	2/19 (11%)	< 0.001
Source: Sponsor's NDA submission (pages 78-81, Volume 42; pages 87-88, Volume 45)			
¹ p-value is the comparison between Tradename and Placebo groups, and is based on Cochran-Mantel-Haenszel test adjusting for center.			

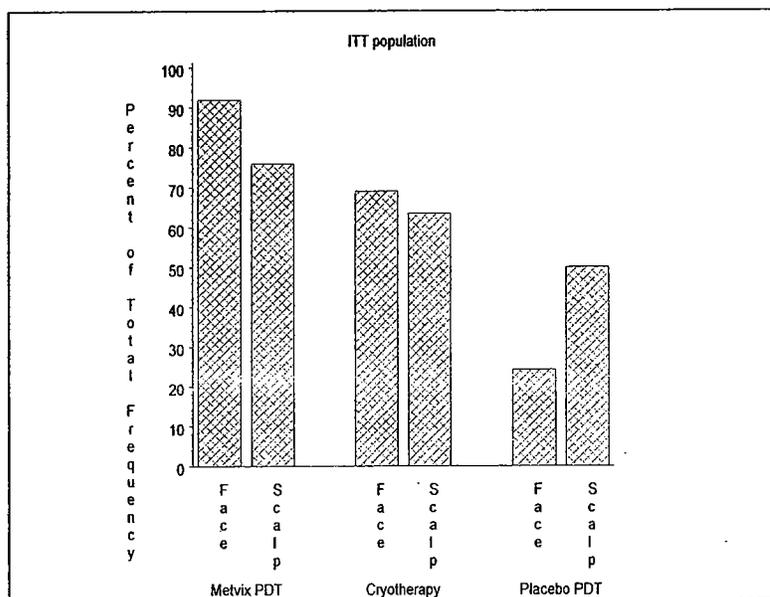
As indicated in the table above, Tradename PDT is statistically superior to placebo-PDT (p-value < 0.001).

The response rate of grade 1 (thin) lesions was 95% in the Tradename[®] PDT group and 34% in the placebo PDT group. The response rate of grade 2 (moderately thick) lesions was 79% in the Tradename[®] PDT group and 23% in the placebo PDT group.

In the Tradename[®] PDT group lesion response rates were higher in the smaller lesions (90% and 84% for 0-10mm and 10-20 mm, respectively) than in the largest lesions (67% for lesions >20 mm). In the placebo group, 32% of lesions 0-10 mm and 8% of lesions 10-20 mm responded. Only one lesion >20 mm was given placebo PDT.

Figure 3 (Figure XI.): Lesion complete response by lesion location

APPEARS THIS WAY
ON ORIGINAL



The response rate for lesions located on the face was 92% in the Tradename[®] PDT group, 69% in the cryotherapy group and 24% in the placebo PDT group. The response rate for lesions located on the scalp was 76% in the Tradename[®] PDT group, 64% in the cryotherapy group and 50% in the placebo PDT group.

Reviewer's comment: *In the placebo group, a response rate of 50% for lesions located on the scalp vs. 24% for facial lesions is not consistent with the trend for the active drug; however, may result from the more effective curettage on scalp lesions.*

The patient complete response rates for the PP population were similar to those of the ITT population.

Efficacy Conclusion

In Study PC T305/99, 204 patients entered and 200 were treated. Randomization was as follows: 88 patients in Tradename[®] PDT study arm, 23 in the placebo PDT study arm, and 89 to cryotherapy. The primary variable was the patient complete response, i.e. percentage of patients with all lesions in complete response, assessed three months after two PDT treatment sessions that were one week apart. Based on Cochran-Mantel-Haenszel test, Tradename[®] PDT demonstrated statistical superiority over placebo PDT (p-value <0.001) in complete patient response in the ITT population. At baseline, 31% (34/111) of the enrolled patients had 4 to 10 lesions, 44% (49/111) of patients had less than 4 lesions, and only 18% (20/111) had more than 10 lesions present. When only patients with 4 to 10 AKs are considered, although statically significant over vehicle, the efficacy decreases with a response rate of 67% vs. 0 for vehicle with p-value = 0.0075).

Study PC T305/99 was not well controlled in that blinding was more problematic. Blinding is difficult due to the phototoxic nature of the PDT therapy and blinding was further compromised since the same investigator administered the treatment and provided the efficacy evaluation. The use of local anesthetics and/or analgesics may also serve as an additional source of breaking the

blind. According to a communication received from the Sponsor by the Division on July 24, 2002, local anesthetics were used in 12 of 88 patients on TRADENAME-PDT and none of the vehicle-PDT patients received local anesthetics. At the time of this written review, the impact on efficacy and safety reporting is unknown. Subgroup analysis should address: 1) the number of complete responders in this group, 2) timing of administration in relationship to drug-device therapy and first or second sessions, 3) by center distribution of these patients, 4) number of lesions per patient (this is important for the Australian study if these patients had only 1, 2, or 3 lesions or were in the 4-5, 6-7, 8-10 or higher lesion groups), and 5) lesion location (face or scalp).

The cryotherapy study arm was not considered in the efficacy evaluation because two pivotal studies with cryotherapy arms would be needed to substantiate efficacy results, after randomization, the cryotherapy study arm was unblinded (due to the nature of the treatment), and freezing time was inadequate (e.g., freeze time range was 2 seconds to 1 minute 30 seconds with a mean of 13 seconds).

Indication #1 Treatment of Actinic Keratosis

This study was designed to compare the efficacy and tolerability of PDT using Tradename® cream, conventional cryotherapy and PDT using placebo cream in the treatment of AK lesions.

**Reviewer's Trial # 3 Sponsor's Protocol PC T302/99
(conducted in Denmark and Norway)**

Trial Dates: June 7, 1999 - January 4, 2000

Title: "A Multicenter Phase III Double Blind Study of Photodynamic Therapy With P-1202 Cream 160 Mg/G Or Placebo Cream In Patients With Actinic Keratosis "

Objective Rationale

The primary objective is to compare the rate of patient response graded as "excellent" after photodynamic therapy using P-1202 cream to photodynamic therapy using placebo cream.

Secondary objectives are to describe the patients in whom fewer than 75% of the lesions show complete response, lesion response rates, cosmetic outcome and adverse events.

Design

Prospective, stratified, randomized, comparative, double blind multicenter study. The actinic keratosis lesions will be treated with photodynamic therapy using P-1202 or placebo cream.

Population/Procedures

Inclusion/exclusion criteria and study procedures were similar to those employed in studies PC T 305/99 and PC T 306/99 except for the following:

- There were no restrictions on the number or thickness of lesions for entry; however, in patients with more than 10 eligible lesions, the 10 randomly chosen lesions were to be treated.
- The diagnosis was to be based on clinical signs and symptoms and, where needed, on histology.
- Only one PDT session was performed for lesions on the face or scalp. For all other lesions, the PDT treatment will be repeated one week after the initial treatment session irrespective of the features of the lesions.
- Number of lamps provided and used was not indicated.

- Thick keratotic lesions were permitted. Due to the more solid consistency of the lesion a cut-off technique with the point of a needle at the base of the lesion could be used in addition to gently scrapping the surface.
- As in Study 305, the investigator prepared the lesions, administered the light, and evaluated efficacy.
- Independent assessment of photographs was performed for complete response and cosmetic outcome because for a portion of the trial, the placebo and the active cream have been filled in tubes with different caps. According to the submission, this could potentially endanger the study randomization process, since the investigator might deduce which tubes contain placebo and which contain active cream. The practical implementation of the randomization procedure was therefore changed. In order to further reduce any bias that may have been introduced into the efficacy assessments, an independent assessor assessed the photographic documentation.

(Amendment #2, July 7, 1999) Appendix H Guideline for independent assessment of photographic documentation was as follows:

The study photographs was collected by the monitoring organisation — . The photographs were presented to the independent assessor in pairs, where each pair consists of a pre-treatment photo and a 3-month follow-up photo. A unique log number identified each pair of photos. The independent assessor was to classify each lesion as “complete response” or “non-complete response.”

Randomization

Ten lesions were to be treated were randomly chosen for treatment in patients with more than 10 lesions. Patients were stratified according to the number of AK lesions into the following strata: 1-3 lesions, 4-7 lesions, 8-10 lesions, and 10 or more lesions. Study medication was be labeled with the patient numbers corresponding to the randomization lists.

Study Endpoints

The Sponsor’s primary efficacy variable is patient response based on lesion assessments performed 3 months after PDT with either P-1202 or placebo. The Sponsor’s secondary end-points was the number of patients in whom 75% or more of the lesions have responded completely at 3 months after PDT with P-1202 or placebo, as assessed by an independent reviewer, based on photographic documentation.

Safety

No direct measurement of Tradename in plasma was performed. Safety was monitored by adverse events reported by the patient, or observed by the investigator. A telephone follow-up to evaluate safety was performed two weeks after treatment.

Study Results

A total of 39 patients were randomized and treated at four study sites (three in Denmark and one in Norway).

Table 11: Investigator, Site No., and No. of patients Enrolled

Investigator	Site No.	No. of patients Enrolled
--------------	----------	--------------------------

	30202	2
Denmark		
	30402	11
Denmark		
	30203	6
Denmark		
	30201	19
Moss, Norway		

Demographics, Evaluability

Number of subjects (total and for each treatment):

	Tradename [®] cream		Placebo	Total
No. planned	20	20	20	
No. randomised and treated	20	19	39	
Males/Females	16/4	9/10	25/14	
Mean age (range)	67 (43 -85)	69 (44-87)	68 (43-87)	
No. analysed for efficacy (ITT)	19	18	37	
No. analysed for efficacy (PP)	20	19	39	
No. completed	19	18	37	

Demographic and Other Baseline Characteristics

Of the 20 patients treated with Tradename[®] cream there were 16 (80%) males and 4 (20%) females. Of the 19 patients treated with placebo there were 9 (47%) males and 10 (53%) females. The mean age was 67 years (range 43 to 85) in the Tradename[®] group and 69 (range 44 to 87) years in the placebo group.

According to the Sponsor (Vol. 1.29, pg. 33) other than the differences in gender distribution, there were no apparent differences between the treatment groups regarding demographic characteristics (age, race, and skin type) at baseline; however, statistical analyses were not performed and presented. All patients were of Caucasian origin. A total of 70% and 68% had a Fitzpatrick skin type II in the Tradename and placebo groups.

Disposition

One patient in each treatment group discontinued prematurely from the study. Patient No. 4013 in the Tradename[®] group withdrew consent before treatment was given. Patient No. 3005 in the placebo group was treated, but withdrew consent before the response evaluation.

Protocol Deviations

For two lesions outside face and scalp, a second PDT was not performed because of local reactions in the treated area (patient No. 4025: ulceration/infection, patient No. 4015: ulceration).

During the study the center in _____ ran out of drug supplies for the stratum 1-3 lesions. Because of this, seven patients were randomized within and received drug assigned for other strata. The decision was made in consultation with the sponsor. In the statistical analyses, these patients were included in the strata corresponding to their actual number of lesions.

For a number of patients, the telephone contact was conducted one week after treatment instead of after two weeks, as specified in the protocol.

Other protocol deviations were defined as follows:

- Light intensity below 70 or above 200 mW/cm²
- Light dose below 60 or above 90 J/cm²
- Application time below 2.5 or above 3.5 hours

A total of 90 lesions were included in the study, 51 lesions were treated with Tradename and 39 with placebo. Nine patients in the active group vs. 8 patients in the placebo group had only one lesion. For Tradename and placebo, patients had two lesion, 5 vs. 4, three lesions, 3 vs. 6 respectively. Four patients, all in the active group, had more than 3 lesions. Most lesions were located on the face or scalp (94% in the Tradename group and 100% in the placebo group). Only four patients were included with more than 4 lesions and no patients had more than 10 lesions.

Table 12 (Sponsor's Table V , Vol. 1.29, pg. 33, modified.): Number of Lesions Per Patient)

Treatment	No. of Patients	No. of Lesions
	n	Sum
Tradename	20	51
PDT Placebo	19	39
Total	39	90

Table 13 (Statistical Table 4): Efficacy Results for Study 302

Efficacy endpoint	Tradename (n=19)	Placebo (n=18)	Comparison	
			Sponsor ¹	Reviewer ³
Percent of patients with 100% of lesions cleared	11 (58%)	2 (11%)	N/A	<0.001
Percent of patients with excellent lesion response	11 (58%)	2 (11%)	(20%, 73%)	< 0.001
Lesion complete response rate ²	32/49 (65%)	6/36 (17%)	N/A	<0.001
Source: Sponsor's NDA submission (pages 35-38, 55, Volume 49).				
¹ Sponsor's results are based on 95% confidence interval for the difference (i.e. Tradename – placebo).				
² Calculation is based on the number of lesions treated.				
³ p-value is based on Cochran-Mantel-Haenszel test adjusting for site.				

Tradename-PDT is statistically superior to placebo-PTD (p-value <0.001); however, the efficacy signal is not clear due to the small number of patients treated and not supported by a second placebo controlled study at the same dosing regimen of one Tradename-PDT treatment session for facial lesions.

Independent Reviewer Report (Study dates June 6, 1999 to January 4, 2000. Report Completion Date March 10, 2000. Addendum Date December 6, 2000)

The independent review was conducted under a separate protocol and the data were not included in the NDA for review by the Division although according to Amendment 2, the Sponsor's secondary efficacy was changed to include the results of the photographic assessment.

According to the Addendum to the Clinical Trial Report (Vol. 1.29, pg. 70), the overall patient excellent response rate was 38% for Tradename and 28% for the placebo group as compared to the 58% and 11% respectively in the clinical evaluation. The Sponsor concluded that the assessment of AKs based on photographic documentation did not provide a reliable outcome.

Reviewer's comments: *These data should have been submitted to the Division for review; however, this study is not considered pivotal and the study design does not support the dosing regimen of the U.S. and Australian studies. The Sponsor's rationale for differences in efficacy is that thin lesions are better felt than seen and are missed on photographs and that color changes from active treatment is difficult to distinguish from small residual lesions. The rationale for Amendment 2 was to find out whether bias may have been introduced into the efficacy assessment.*

Efficacy Conclusion

The efficacy signal is not clear due to the small number of patients treated and not supported by a second placebo controlled study at the same dosing regimen of one Tradename-PDT treatment session for facial and scalp lesions. Blinding was also problematic in this study.

D. Efficacy Conclusions

In two clinical trials (one conducted in the U.S. and the other conducted in Australia), two photodynamic therapy sessions conducted with Tradename Cream has shown superiority over placebo cream plus illumination using a two-stage process in treatment of actinic keratoses (p-value <0.001). The two-stage process is repeated twice 7 days apart and involves the following: (1) superficial preparation of the lesions followed by application of Tradename[®] 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 and total light dose of 75 J/cm² using the CureLight lamp.

In contrast to the U.S. study where all patients had 4-10 AK lesions at baseline, in the Australian study, 63% (55/88) of the patients in the active group had less than 4 lesions. According to the Division's Statistician, when only subjects with 4-10 AK lesions were analyzed Tradename is statistically better than placebo (i.e., patient complete response rates 67% vs. 0 for Tradename vs. placebo with p-value = 0.0075).

Two additional Phase 3 studies (Studies 301 and 302) were submitted by the Sponsor in support of the safety and efficacy of one photodynamic treatment session for lesions located on the face and scalp using Tradename Cream in a two-stage process. Except for the two-stage process of lesion preparation/Tradename application for 3 hours and illumination, these Studies 301 and 302 were neither identical to each other nor identical to the Phase 3 studies discussed above. The

sample size was small in Study 302 and Study 301 has no placebo arm making it difficult to assess a reliable estimate of treatment effect.

Meeting minutes (pg. 6) from the pre-IND/EP-2 meeting indicates that the Sponsor was advised to clarify how investigators will be instructed to decide whether a given lesion needs re-treatment at Week 2. The Sponsor did not provide instructions in any of the clinical trials presented on how to determine whether a lesion needs re-treatment. All patients were scheduled to receive either one or two Tradename-PDT treatments at a predetermined treatment regimen. The Sponsor's proposed labeled Dosage and Administration Section states that treatment may consist of one session or two session 7 days apart; however supportive data for one treatment session is inadequate. Additionally, inflammation can be expected 7 days post-treatment at the treatment sites making an accurate assessment regarding re-treatment difficult.

The Sponsor has proposed new safety procedures to prevent cross-contamination between patients with use of the device at the time of this review it is unknown whether efficacy might be impacted.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Several outstanding unresolved safety issues are listed below and discussed in depth in the section that follows.

- Biochemical and hematologic monitoring data from patients exposed to the proposed dosing regimen of 2 treatment sessions 7 days apart were not submitted to the NDA. Slight increases in serum ALT (although not statistically significant in female minipigs) were observed. Additionally, there has been no direct measurement of methyl-aminolevulinat e HCl in serum due to a putative instability in this medium.
- During conduct of the clinical trials, appropriate procedures to prevent between patient cross-contamination with use of the light diode and horseshoe-positioning portions of the device were not communicated to the investigators from the Sponsor. Appropriate procedures to prevent between patient cross-contamination and have not been adequately addressed and remains an outstanding safety issue.
- An unusually high contact sensitization potential for Tradename Cream (methyl ALA) as been identified in normal human subjects. Protection of personnel handling the medication is needed for labeling. Sensitization potential was not demonstrated in a similar ALA drug product (Levulan) that does not contain a methyl group. Cross sensitization between the already approved ALA product are unknown. Cross sensitization with endogenous ALA although thought to be unlikely is unknown and is a concern.
- The incidence of sensitization is expected to be greater when applied to diseased skin where the epidermal barrier has been further compromised by curettage; therefore, data supporting safety re-treatment are needed. Due to the unusually high contact sensitization potential for

Tradename Cream, re-treatment data are needed and a safety data base of at least 300 are needed to detect 1% AE incident needed to properly label the drug product.

- The photosensitization potential has not been studied and is unknown.
- Safety data for overlapping treatment fields in patients with multiple lesions are needed. Additionally, safety data should have been presented for per patient treatment duration, number of lamps needed simultaneously, maximum application time for Tradename, and maximum number of treatment fields.

Reviewer's comments:

The Sponsor did not provide disinfection/sterilization procedures to be followed for between patient use of the device during conduct of the clinical trials. According to a fax received from the Sponsor on July 24, 2002, all 4 U.S. centers used alcohol swabs or wipes to clean the light measuring probe. In the Australian study the procedures varied from none at 2 centers to use of chlohexidine spray, Viraclean, isopropyl alcohol wipes or benzalkonium chloride spray. Where performed, the frequency of the disinfection procedures varied and included form after every patient to occasionally.

B. Description of Patient Exposure

The amount of drug product applied was not provided or addressed by the Sponsor in the study report, case report forms, data listings, nor in the integrated summary of safety. The Sponsor should provide these data. PK studies were limited to use of one gram; therefore, in the labeled drug product, only a total of 1 gram per treatment session should be recommended.

Actinic Keratosis Indication

Only 132 patients were exposed to Tradename Cream-PDT for the AK indication at the proposed labeled regimen (i.e., 2 applications 7 days apart) in the Phase 3 Study PC T305/99 (conducted in Australia) and PC T306/99 (conducted in the U.S.), 91 and 41 patients respectively. This number of patients is far below the short-term safety database of 300 to 600 recommended in the ICH E1A guidance. Actinic keratosis is a chronic condition usually in middle age or older people on sun-exposed regions of the body. The Sponsor was referred by the Division to ICH-E1A guidance for information on the number of study subjects needed for an adequate assessment of the safety profile of a drug product intended for treatment of a chronic condition on at least two occasions (pre-IND meeting #4478 held on August 2, 1999 and pre-IND (EP-2) meeting held on June 22, 2000).

Studies identified by the Sponsor as Phase 3 studies (PC T306/99, PC T305/99, PC T302/99, and PC T301/99) had two different treatment regimen. Only face and scalp lesions were treated and all lesions were treated twice at 7 days apart for patients enrolled in studies PC T306/99 and PC T305/99. For studies PC T302/99, and PC T301/99, lesions were treated differently by location (e.g., one treatment session for lesions located on the face and scalp and two treatment sessions for lesions located elsewhere). See the table that follows for summary of Phase 3 studies submitted in the NDA.

Table 14 (Statistical Table 1.): Overview of the Four Phase 3 Trials

Study	Study conducted	Patients inclusion	Treatment arms, n	Comments on treatments
-------	-----------------	--------------------	-------------------	------------------------

Pivotal Trials				
306	US (6/00-2/01)	4-10 mild to moderate AK lesions on the face or scalp	Tradename PDT: 42* Placebo PDT: 38	Patients were treated with two treatment sessions with 7 days apart
305	Australia (3/00-12/00)	Unlimited mild to moderate AK lesions on the face or scalp	Tradename PDT: 91 Placebo PDT: 23 Cryotherapy: 90	PDT: two sessions with 7 days apart Cryotherapy: one treatment session with one freezing cycle
Supportive Trials				
302	Europe (6/99-1/00)	1-10, any grades of AK lesions located on any locations	Tradename PDT: 20 Placebo PDT: 19	PDT: only one session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations
301	Europe (4/99-11/99)	1-10, any grades of AK lesions located on any locations, suitable for cryotherapy	Tradename PDT: 102 Cryotherapy: 100	PDT: only one session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations. Cryotherapy: one treatment session with two freezing cycles

* Patient received only one treatment due to AE; however, was included in efficacy for 2 treatment session regimen

Study PC T305/99 was amended to include patients with more than 10 lesions; paradoxically, the majority of the 88 patients randomized to active drug, 63% (55/88) had less than 4 lesions at baseline.

The number of lesions per patient in the Placebo-Controlled AK studies follows in the table below; however, this includes patients enrolled in Study 302/99 who received only one treatment session for lesions located on the face and scalp.

Table 15 (Sponsor's Table 1, Vol. 1.37, pg. 43): Number of Lesions per Patient in Placebo-Controlled AK Studies Safety Population

Number of Lesions per Patient	Tradename-PDT (N=149) n (%)	Placebo-PDT (N=80) n (%)	Overall (N=229) n (%)
1	31 (21)	15 (19)	46 (20)
2	30 (20)	10 (13)	40 (17)
3	10 (7)	8 (10)	18 (8)
4	22 (15)	10 (13)	32 (14)
5	10 (7)	13 (16)	23 (10)
6	12 (8)	5 (6)	17 (7)
7	9 (6)	6 (8)	15 (7)
8	7 (5)	4 (5)	11 (5)
9	8 (5)	4 (5)	12 (5)
10	4 (3)	4 (5)	8 (3)
11-28	6 (4)	1 (1)	7 (3)
Number of lesions (sum)	669	355	1024

Data Source: Statistical Table 2.7, Appendix 1.

As noted above, the number of AK lesions per patient was similar in Studies 302/99 and 305/99. The protocol of Study 306/99 stipulated that all patients must have 4-10 AK lesions; therefore, the number of lesions per patient was higher in this study than in the other placebo-controlled AK studies.

Drug accountability reporting for the NDA was not provided. No data was presented on the number of tubes allotted per patient, total amount of drug applied per patient, although lesion data (size, location, and number) were tabulated. Instructions were to apply a layer of Tradename[®] cream about 1 mm thick to the lesion and the surrounding 5 mm of normal skin. Drug (active and placebo) was supplied to study sites in 2-gram collapsible aluminum tubes. No known record of the number of tubes allotted or dispensed per patient was submitted to the NDA.

BCC Indication

Sponsor is conducting studies using Tradename-PDT in treatment of basal cell carcinoma. At NDA submission, the Sponsor only submitted serious adverse events from the BCC studies. The Sponsor did not submit needed data from the BCC studies to support safety of Tradename-PDT.

In a response (dated June 28, 2002) from the Sponsor to a query from the Division, the Sponsor submitted data from Study PC T205/98, "A Pivotal Study of Photodynamic Therapy with Tradename[®] Cream 160mg/g in Patients with Basal Cell Carcinoma Unsuitable to Traditional Therapy", in which 94 patients with BCC were treated with the two-treatment regimen. Blood samples were drawn at baseline, 2 weeks after the first treatment, and 15 weeks after the first treatment. According to the communication, there were no clinically significant changes in liver enzyme values or bilirubin; however, clinically significant was not defined.

The Sponsor submitted scatter plots for serum ALAT values at visit 4 (2 weeks after the first PDT) and visit 7 (15 weeks after first PDT) plotted against baseline values for ALAT, ASAT, and bilirubin. No other chemical or hematological data were submitted. With suggestion of possible liver toxicity with repeat topical drug application in the minipig study, coupled with lack of systemic PK absorption data systemic laboratory data are needed for risk benefit assessment in patients with AKs. It should be noted that there is no placebo arm to allow the adverse event rate in the drug-treated group to be compared directly with a background rate in the patient population being studied. Laboratory values were not submitted for review; therefore, the Sponsor's response did not adequately address this informational need regarding safety of Tradename[®] Cream.

According to Table 1 (Table of Studies in the ISS, Vol. 1.37), clinical trial reports for the following studies were not included in the NDA per agreement with the FDA: PCT T203/98, PCT T303/99, PCT T304/99, PCT T307/00, PCT T308/00, PCT T310/00, and PCT T208/98A. However, no such agreement was noted in any of the meeting minutes. Actually, according to the Pre-NDA meeting minutes (pg. 8), the Sponsor was advised that the Division prefers a safety report including all subjects who received treatment in each of the studies listed in Table 14 (the AK studies) and in Table 19 (Table Shell for BCC Data Presentation in the ISS) on page 63 of the briefing package, listing all adverse events, the degree of severity, and the percentage of subjects who experienced each type of event. These data are again being requested.

According to Table 1 (Table of Studies in the ISS, Vol. 1.37) there were no deaths, other SAEs, or discontinuations due to AEs for Study PC T205/98, PC T 101/97, PC T 308/00, PC T 107/01,

PC T 108/01, PC T 208/98, and PC T 212/00. These studies are ongoing except for PC T 101/97, PC T 107/01, and PC T 212/00; however, these three studies are Phase 1 studies conducted on normal skin in healthy subjects.

According to the submission (Vol. 1.37, pg. 17) under compassionate use (Study PC T001/97), there are >1000 patients with AK and a variety of non-melanoma skin cancer that have been treated in an open-label, uncontrolled study conducted at

However, this study was not conducted under Good Clinical Practice (GMP) and in compliance with International Conference of Harmonization (ICH) on GMP. The Sponsor was advised at Meeting #4478 (held between the Sponsor and the Division on August 2, 1999) that anecdotal information has little regulatory utility and that collecting and analyzing data from an open label study retrospectively is subject to selection and recall bias.

C. Methods and Specific Findings of Safety Review

Local, systemic, device procedures and dermal safety studies were reviewed. Phototoxicity studies were waived. The following table provides an overview of adverse events that occurred in the placebo-controlled trials. Local AEs and non-local AEs are then addressed separately.

**Table 16 (Sponsor's Table 25. Vol. 1.37, pg. 48):
Overview of Adverse Events in Placebo-Controlled AK Studies**

Variable	Safety Population	
	Tradename-PDT (N=149) n (%)	Placebo-PDT (N=80) n (%)
Patients with any adverse event	126 (85)	37 (46)
Number of adverse events	387	75
Patients with SAEs	2 (1)	0 (0)
Number of SAEs	2	0

Data Source: Statistical Table 2.11, Appendix 1.

Note: The table above also includes data from patients enrolled in Study 302/99 that received one or two treatments depending on the location of the lesion.

Table 17 (Sponsor's Table 17, Vol. 1.37, pg. 51): Overview of Local and Non-Local Adverse Events in Placebo-Controlled AK Studies Safety Population

Variable	Tradename-PDT	Placebo-PDT
	(N=149) n (%)	(N=80) n (%)
Patients with Any Adverse Event	126 (85)	37 (46)
Local Adverse Events		
Patients with local adverse event	118 (79)	29 (36)
Number of local adverse events		
1	37 (25)	15 (19)
2	28 (19)	7 (9)
3 or 4	32 (21)	7 (9)
5 or 6	19 (13)	0 (0)
7 to 10	2 (1)	0 (0)
Non-Local Adverse Events		
Patients with non-local adverse event	42 (28)	15 (19)

Number of non-local adverse events		
1	23 (15)	9 (11)
2	14 (9)	3 (4)
3 or 4	5 (3)	3 (4)

Data Source: Statistical Table 2.12, Appendix 1.

The proportion of patients in Study 302/99 who experienced adverse events (42%) was smaller than the proportion of patients in Study 305/99 (78%) and Study 306/99 (75%). This was true for both the Tradename-PDT and the placebo-PDT treatment groups. Patients in Study 302/99 received 1 treatment, compared to the 2 treatments received by large majorities of patients in Studies 305/99 and 306/99.

The proportions of patients who experienced local adverse events were similar in Studies 305/99 and 306/99 (71% and 66%, respectively). In both of these studies, over 90% of patients attended 2 treatment visits. More than 95% of patients in Study 302/99 attended only 1 treatment visit, and 39% of these patients experienced local adverse events. This pattern was repeated for patients in the Tradename-PDT and placebo-PDT treatment groups. Studies 305/99 and 306/99 appear to have similar distributions of the numbers of local adverse events per patient.

Non-local adverse events were also experienced by higher proportions of patients in Studies 305/99 and 306/99 (30% and 26%, respectively) than in Study 302/99 (8%). In Study 305/99, 32% of patients treated with Tradename-PDT had non-local adverse events, compared to 22% of patients treated with placebo-PDT. In Study 306/99, there was no difference in the proportion of patients in the 2 treatment groups who experienced non-local adverse events (26%).

The quality and reliability of systemic as well as the local AE data collected in the U.S. study (306/99) may not be reliable in that these data may not have been collected based on observations of a qualified investigator. Additionally, the use of local anesthetics and analgesics (topical or oral) may dilute the intensity reported for some AEs in the pooled safety data. This use of local anesthetics and analgesics perhaps explains the lower incidence of reported AEs for the second treatment session and 54% rate of local AEs for the vehicle group noted in the table below.

According to a faxed communication received from the Sponsor on July 24, 2002, during training sessions investigators were instructed not to use local anesthetics, except in special cases when specifically requested by the patient. These were recorded as concomitant medications.

In the Australian study 305/99, 14% (12 of 88) patients on active-PTD received local anesthetics and 18 % (16 of 88) received topical or oral analgesics. None in the vehicle-PDT group (0 of 23) received local anesthetics or analgesics (topical or oral). In the U.S. study 306/99, 1 of 42 patients on active-PTD had local anesthetic administered and 11 received analgesics while for the vehicle-PDT study arm, 5 of 38 had local anesthetics and 1 receive analgesics.

Table 18 (Statistical Table 6): Overall Incidence of Adverse Events: Studies 305 and 306 Combined

Events	Tradename PDT (n=130)	Placebo PDT (n=61)	Cryotherapy (n=89)
Subjects with at least one adverse event	114 (88%)	33 (54%)	43 (48%)
Total adverse events	488	76	89
Total local adverse events	301	44	49
Local adverse events by intensity:			
Mild: total events	149	38	36
Moderate: total events	123	6	7
Severe: total events	29	0	6
Total treatment-related local AEs	298	41	46
Adverse events by intensity:			
Mild: total events	146	36	33
Moderate: total events	123	5	7
Severe: total events	29	0	6
Subjects with adverse events resulting in discontinuation	2 (1.5%)	0	0
Serious adverse events	2 (1.5%)	0	0
Deaths	0	0	0
Source: Sponsor's NDA submission (pages 50-52, Volume 42; pages 55-58, Volume 45).			

Local Safety

In the placebo-controlled studies, the proportion of patients treated with Tradename-PDT with adverse events (88%) was higher (and perhaps was even higher) than the proportion of patients with placebo-PDT with adverse events (54%). Most adverse events in the Tradename[®] PDT were associated with treatment related local reactions such as burning sensation, erythema, crusting and pain. Erythema lasted for a median of 18 days and symptoms such as burning sensation, crusting, blisters and pain had a median duration of 2-4 days. The severity of these symptoms was reported mostly as mild to moderate. Two patients stopped illumination due to adverse events, and another patient did not undergo the second treatment due to adverse event from the first treatment.

Local adverse events were presented for treatment sessions as first treatment and second treatment for Studies 306 and 305; however, the intervals are not defined and any adverse effects of the Tradename Cream alone can not be discerned. With photodynamic therapy, there are three distinct periods in which adverse events should be assessed for the incidence and severity of adverse events. In contrast to other topical medications in which one period is relevant, the period of drug administration, three periods should have been assessed for Tradename[®] PDT. Adverse event data should have been collected [pre-PDT] the period from Tradename application until light administration, [peri-PDT] the period during and shortly after illumination, and [post-PDT] the period from shortly after illumination to end-of-follow-up. These data are important to be able to distinguish symptomatic actinic keratoses from the effect of PDT-treatment adverse events.

Anesthetic and/or analgesic use may have influenced the lower AE incidence reported for the second treatment profile as noted in the table that follows.

Table 19 (Modified from Sponsor's Table 55, Vol. 1.22, pg. 119, Study PC T306/99 and Sponsor's Table 48, Vol. 1.25, pg. 107, Study PC T305/99): Patients with Local Adverse Events, Safety/ITT Population

Treatment Group	Treatments	No. of Patients	Local Adverse Event				No. of Local AEs Sum
			No		Yes		
			N	%	N	%	
Study 306/99							
Tradename PDT	First treatment	42	6	14%	36	86	101
	Second treatment	39	11	28	28	72	56
Placebo PDT	First treatment	38	24	63	14	37	22
	Second treatment	38	32	84	6	16	10
Study 305/99							
Tradename PDT	First treatment	88	24	27	64	73	134
	Second treatment	80	27	34	53	66	126
Placebo PDT	First treatment	23	16	70	7	30	10
	Second treatment	22	16	73	6	27	8

No data were submitted addressing opacity of Tegaderm® (3M) that was used to occlude lesions after test drugs (Tradename or vehicle) had been applied. According to the protocol (Vol. 1.22, pg. 17) no special precautions were necessary in the 3-hour interval between drug application to removal, or after treatment; however, adverse event profile data were not presented to substantiate this claim.

**APPEARS THIS WAY
ON ORIGINAL**

Table 20 (Sponsor's Table 14, Vol. 1.37, pg. 47): Descriptions of Photodynamic Therapy Applied to Lesions on Patients in Placebo-Controlled AK Studies
Safety Population

Characteristic	Tradename-PDT N=1232	Placebo-PDT N=665	Overall N=1897
Application time (h:min)	N=1232	N=664	N=1896
Mean (Std)	3:13 (0:17)	3:11 (0:14)	3:12 (0:16)
Range	2:10, 4:45	2:56, 4:28	2:10, 4:45
Median	3:07	3:05	3:06
Illumination time (min:sec)	N=1222	N=664	N=1886
Mean (Std)	9:55 (3:40)	9:24 (2:48)	9:44 (3:23)
Range	0:43, 27:50	4:30, 23:40	0:43, 27:50
Median	8:50	8:30	8:50
Light intensity (mW/cm ²)	N=1210	N=660	N=1870
Mean (Std)	142 (44)	147 (36)	144 (41)
Range	37, 386	37, 285	37, 386
Median	145	153	148
Light dose (J/cm ²)	N=1210	N=660	N=1870
Mean (Std)	77 (9)	78 (6)	77 (8)
Range	4, 124	22, 125	4, 125
Median	77	77	77
Light field diameter (mm)	N=1223	N=665	N=1888
Mean (Std)	43 (7)	42 (6)	43 (7)
Range	25, 55	25, 55	25, 55
Median	40	40	40

Data Source: Statistical Table 2.10, Appendix 1.

The number of total treatment duration, treatment fields, and lamps used was not addressed. According to the protocol, 2 lamps were supplied to each center. At the Pre-IND meeting, the Sponsor projected that each treatment takes about 10 minutes. The Sponsor estimated that no patient would need more than half an hour. As previously noted, total treatment duration data per patient were not collected and presented.

For Study 305/99 treatment fields were recorded and up to 6 field per patient was permitted per protocol yet the majority of patients had less than 4 lesions. The number of treatment field was not addressed in the U.S. study (306/99) where all patients had 4 –10 lesions. The Sponsor did not present a strategy, perhaps staggering the application of cream to various groups of lesions when a patient has many, as encouraged Division. There is no precautions, efficacy or safety data regarding overlapping treatment fields or the necessity of overlap avoidance.

Phase 3 studies are to simulate as closely as possible post-approval use; however, to this reviewer, the actual conduct of these studies were not as per the written protocol. The technique was demonstrated to each investigator and apparently this significantly supplemented the written protocol. The illumination time presented in table above presents per lesion totals. As noted, application time range of 2:10 - 4:45 (active) and 2:56- 4:28 (placebo) would infer some patients may have had more than 13 hours of application or illumination time (even with availability of two lamps); the Sponsor did not submit sub-group analyses of these safety (and efficacy) variables nor were these variables addressed per written protocol.

Adverse events in the table that follows are tabulated as the percentage relative to total local AEs. The Sponsor has been asked to calculate the percentages for adverse reactions based on occurrence(s) per patient and provide 95% confidence interval. These results may have been under-reported.

Table 21 (Statistical Table 7): Summary of Local Adverse Events

Events	Tradename PDT (n=130)	Placebo PDT (n=61)
Subjects with at least one adverse event	114 (88%)	33 (54%)
Total adverse events	488	76
Total local adverse events	301	44
# of local adverse events:		
Burning sensation skin	70 (23%)	8 (18%)
Erythema	64 (21%)	12 (27%)
Crusting	20 (7%)	6 (14%)
Pain skin	29 (10%)	3 (7%)
Blisters	14 (5%)	2 (5%)
Oedema skin	21 (7%)	1 (2%)
Stinging skin	25 (8%)	2 (5%)
Skin ulceration	7 (2%)	0
Skin peeling	14 (5%)	2 (5%)
Pruritus	8 (3%)	2 (5%)
Itching	9 (3%)	0
Bleeding skin	11 (4%)	2 (5%)
Irritability skin	1 (< 0.5%)	0
Milia	1 (< 0.5%)	0
Hyperkeratosis	0	1 (2%)
Skin infection	3 (1%)	1 (2%)
Dermatitis contact	1 (< 0.5%)	0
Photosensitivity toxic reaction	1 (< 0.5%)	0
Rosacea	1 (< 0.5%)	0
Skin hyperpigmentation	1 (< 0.5%)	0
Skin disorder	0	1 (2%)
Skin inflammatory NOS	0	1 (2%)
Source: Sponsor's NDA submission (pages 97-99, Volume 42; pages 57-58, Volume 45).		

- In Tradename PDT group, a higher percentage of patients had at least one adverse event as compared with placebo arm (88% vs. 54%, Table 6).
- Most adverse events in Tradename group were local adverse events. Among them, 99% of the events (i.e. 298/301) were treatment-related and most were mild to moderate in severity. Two subjects (1.5%) in Tradename group discontinued the treatment due to adverse events (Table 6).
- Burning sensation skin and erythema were the most common local adverse events for Tradename and placebo PDT (23%, 21% in Tradename and 18%, 27% in placebo, Table 7).

Table 22 (Sponsor's Table 3) that follows shows the intensity of local adverse events related to study treatment and reported by $\geq 1\%$ of all patients. The majority of events related to Tradename-PDT treatment were mild or moderate in intensity. None of the related local adverse events in the vehicle-PDT treatment group were severe, and there were cases of moderate

burning sensation in skin, skin pain, and peeling skin. It is unknown whether the AEs reported in the vehicle group were secondary to the illumination with the device, vehicle, or to curettage because AEs were not collected and reported in a manner that a distinction could be ascertained. In the Tradename-PDT treatment group, related local adverse events that were reported as severe by >1 patient were: burning sensation in skin, erythema, skin pain, and skin edema. Statistical Table 2.14 summarizes data on the intensity of local adverse events that were considered related to study treatment.

The majority of local adverse events that were considered related to study treatment were classified as having mild or moderate intensity in each of the 3 placebo-controlled AK studies. Five (5) percent of the reported local adverse events were rated as of severe intensity in Study 306/99, compared to 12% in Study 305/99 and none in Study 302/99.

Table 22 (Sponsor's Table 3.Vol. 1.37, pg. 45): Intensity of Related Local Adverse Events Reported by $\geq 1\%$ of All Patients in Placebo-Controlled AK Studies
Safety Population

Adverse Event (Preferred Term)	Tradename-PDT (N=149)				Placebo-PDT (N=80)			
	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Burning sensation skin	33 (22)	30 (20)	10 (7)	73 (49)	7 (9)	2 (3)	0 (0)	9 (11)
Erythema	33 (22)	29 (20)	4 (3)	66 (44)	12 (15)	0 (0)	0 (0)	12 (15)
Skin pain	12 (8)	17 (11)	8 (5)	37 (25)	5 (6)	2 (3)	0 (0)	7 (9)
Stinging skin	12 (8)	12 (8)	1 (1)	25 (17)	2 (3)	0 (0)	0 (0)	2 (3)
Crusting	13 (9)	6 (4)	1 (1)	20 (13)	6 (8)	0 (0)	0 (0)	6 (8)
Skin edema	11 (7)	9 (6)	2 (1)	22 (15)	1 (1)	0 (0)	0 (0)	1 (1)
Blisters	9 (6)	4 (3)	1 (1)	14 (9)	2 (3)	0 (0)	0 (0)	2 (3)
Peeling skin	8 (5)	6 (4)	0 (0)	14 (9)	1 (1)	1 (1)	0 (0)	2 (3)
Bleeding skin	6 (4)	3 (2)	1 (1)	10 (7)	2 (3)	0 (0)	0 (0)	2 (3)
Skin ulceration	2 (1)	8 (5)	1 (1)	11 (7)	1 (1)	0 (0)	0 (0)	1 (1)
Itching	4 (3)	5 (3)	0 (0)	9 (6)	0 (0)	0 (0)	0 (0)	0 (0)
Pruritus	5 (3)	2 (1)	0 (0)	7 (5)	1 (1)	0 (0)	0 (0)	1 (1)
Skin infection	0 (0)	3 (2)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)

Data Source: Statistical Table 2.14, Appendix 1.

In the majority of cases, local adverse events were considered related to study treatment. Therefore, only related local adverse events were presented by the Sponsor; however, all AEs should have been reported.

The incidence of local adverse events considered related to study treatment and reported by $\geq 1\%$ of all patients was presented by the Sponsor. The local adverse events considered related to treatment in 10% or more of patients who were treated with Tradename-PDT were burning sensation in skin, erythema, skin pain, stinging skin, crusting, and skin edema. The incidences of related local adverse events were, as expected, considerably higher in patients treated with Tradename-PDT than in patients treated with placebo-PDT. Erythema (15%) was the most common related local adverse event in the placebo-PDT treatment group, while burning sensation in skin (49%) was the most common related local adverse event in the Tradename-PDT treatment group.

According to the Sponsor, the outcome of all related local adverse events reported by $\geq 1\%$ of patients with intensities that were moderate or severe resolved. Two cases with moderate erythema in Study 305/99 and 1 severe case of erythema in Study 306/99 in the Tradename-PDT treatment group persisted.

Systemic Safety Profile

The table that follows displays the incidence of non-local adverse events reported by $\geq 1\%$ of all patients, including both related and unrelated events. There were only 7 of these adverse events, and the incidence of each event was $\leq 5\%$. Overall, the frequencies of these adverse events were very similar in the 2 treatment groups. Two of these events (tingling skin and application site reaction) were local phototoxic reactions; as expected, these were somewhat less common in the placebo-PDT treatment group than in the Tradename-PDT treatment group. The remaining non-local adverse events reported by $\geq 1\%$ of all patients were headache, malignant skin neoplasm, influenza-like symptoms, surgical intervention, and upper respiratory tract infection.

The 2 instances of malignant skin neoplasm that were considered related to treatment were reported in Study 305/99 (both in the Tradename-PDT treatment group). The malignant skin neoplasm that was classified as having moderate intensity (in Patient 1019) was described by the investigator as having an uncertain relationship to treatment. The investigator's verbatim description of the adverse event is "? SCC in lesion 1." Patient 1004 was diagnosed as having a malignant skin neoplasm with mild intensity. The investigator made the following assessment, "New squamous cell carcinoma" with an uncertain relationship to treatment. These data are presented in Listing 11, Study 305/99.

Table 23 (Sponsor's Table 21, Vol. 1.37, pg. 58): Non-Local Adverse Events Reported by $\geq 1\%$ of All Patients in Placebo-Controlled AK Studies
Safety Population

Adverse Event (Preferred Term)	Tradename-PDT	Placebo-PDT
	(N=149) n (%)	(N=80) n (%)
Tingling skin	8 (5)	2 (3)
Headache	6 (4)	2 (3)
Application site reaction	5 (3)	0 (0)
Malignant skin neoplasm	2 (1)	3 (4)
Influenza-like symptoms	3 (2)	1 (1)
Surgical intervention	3 (2)	1 (1)
Upper respiratory tract infection	2 (1)	2 (3)

Data Source: Statistical Table 2.15, Appendix 1.

The types and numbers of non-local adverse events that were reported differed among the placebo-controlled AK studies. Only 26% of patients in Study 306/99, 30% of patients in Study 305/99 and 8% of patients in Study 302/99 experienced non-local adverse events. In Studies 305/99 and 306/99, some of these non-local adverse events such as tingling skin and

application site reaction should actually be regarded as local phototoxic reactions. A summary of non-local adverse events is shown in Statistical Table 2.15

None of the non-local adverse events were classified as severe. All incidences of tingling skin and application site reaction were considered related to treatment. Other non-local events considered related to study treatment were 5 of 8 incidences of headache and 2 of 5 incidences of malignant skin neoplasm. Most of the treatment related events coded as systemic events were actually to be considered local events. Only one remaining systemic event had a possible relationship to the treatment procedure, i.e. mild dizziness.

Laboratory Monitoring

According to the Sponsor (Vol. 1.37, pg. 179), blood counts and biochemistry were examined in 359 patients in Studies 202/98 (dose-ranging AK study), 203/98 (ongoing BCC study), 204/98 (), and 205/98(ongoing BCC). Of the 229 patients, only 94 patients in Study 205/98 9(BCC study) receiving therapy at least at the 2-session treatment regimen had systemic laboratory monitoring. Study details and laboratory data were not submitted from 205/98 (BCC) for review in support of safety of two-treatment sessions with Tradename-PDT.

Table 24: Summary of the Number Treatment Sessions in Studies with Laboratory Data

Study # , indication, phase	Type of Study	Total # Enrolled	# of Patients with same treatment regimen as Phase 3 (2 treatment cycles 7 days apart)	# of patients with exposure > Phase 3 treatment regimen	Status of Study
202/98 (AK) Phase 2	Dose finding (4 study arms)	112	None*	None	Completed
203/98 (BCC) Phase 2	Dose finding (4 study arms)	141	None (one treatment session repeated at 3 months if required)	36 (18 hours application time)	Ongoing Clinical trial report not available**
204/98 (AK)	Intra-individual Comparative Study	12	None	None	Completed
205/98 (BCC)	Phase 2, open, non-randomized	94	94	Repeat treatment cycle at 3 months if incomplete response	Clinical trial report not available**

*laboratory measured one week after one treatment session

** Purported as per agreement with FDA

According to the submission, few clinically relevant treatment-emergent laboratory abnormalities have been reported. Two clinically relevant laboratory abnormalities were reported in two BCC studies (203/98 and 205/98). Clinically relevant treatment-emergent laboratory abnormalities were not defined and supported data were not submitted for review. The Sponsor reported a raised bilirubin (23.8 µmol/l) level one week after treatment in Study 203/98. In study 203/99, a raised creatinine (132.6 µmol/l) and low hemoglobin of 5.12 g/d after

first treatment cycle in one patient with a return to normal hemoglobin one week after the second treatment cycle (15.1 g/dl).

Study PC T202/98 was a dose-ranging study that did not include a placebo study arm. Biochemical and hematological parameters were assessed at 1-week follow-up after one treatment cycle in 30 patients treated in the 3 hour, 160 mg/g study arm. According to the Sponsor, there were no clinically relevant changes that could be attributed to Tradename treatment. Laboratory assessments were to be described and analyzed to evaluate changes from baseline using non-parametric analysis of variance. In addition, clinically important deviations from baseline or from specified ranges were analyzed by Chi-square analysis to evaluate differences between treatment groups (pg. 26). Table 33: Safety. Laboratory data. Number of patients with changes from baseline greater than 40% and 80% of the reference range are presented in Vol. 1.33. The relevance of this 40% and 80% of the reference range is not clear.

D. Adequacy of Safety Testing

Laboratory monitoring during conduct of the Phase 3 studies should have been performed. Pharm/Tox minipig data submitted for the first time with the NDA suggest possible liver toxicity with repeat dermal application; therefore, systemic laboratory data in humans is needed at the 2-session treatment regimen. Overall, inadequate systemic exposure data have been presented for review to support safety for the drug product. No systemic laboratory monitoring was performed in the pivotal Phase 3 studies at the proposed dosing regimen of two treatment sessions 7 days apart and the Sponsor did not provide a rationale for not performing biochemical and hematological monitoring in the pivotal Phase 3 studies.

A possible liver toxicity signal is detected in the repeated dose minipig study that was submitted for review for the first time with the NDA. The repeated dose minipig study was requested at the end of Phase 2 meeting to support the Sponsor's phase 3 clinical trials. The report for that study was submitted for the first time with the NDA.

According to the Pharm/Tox Reviewer, a dermal study in minipigs was performed, consisting of four sequential treatments at 12-26 day intervals with P-1202 cream applied to intact skin followed by photoactivation. Results in treated skin were limited to marked chronic dermatitis that persisted through the 15-day recovery period. Photoactivation of the areas treated with the drug product resulted in acute wounds. Areas treated with the drug product but not illuminated exhibited slight chronic dermatitis that was mostly reversed in the recovery period.

According to the Pharm/Tox Review, in the 14-day study in rats receiving daily intravenous doses of methyl ALA, increased liver weights were seen at all doses (50-600 mg/kg). At the high dose, equivalent to a human dose of 100 mg/kg or 15 times the maximum clinical dose, increased bilirubin, increased serum ALT, and cholangitis/peri-cholangitis were found. In a study in rats of topically applied methyl ALA as TRADEMARK cream or dilutions thereof, followed by photoactivation and repeated for four treatments at intervals of 10-18 days, increased serum alkaline phosphatase and inflammatory foci in the liver were seen at all doses (60-600 mg/kg). Decreased serum protein and either gross liver enlargement or increased liver weight were seen at 300 and 600 mg/kg. At the high dose, using the clinical TRADEMARK formulation, equivalent to 100 mg/kg or 15 times the maximum clinical dose, serum ALA concentrations were ten-fold higher after the fourth dose than after the first dose.

A study of topically applied TRADEMARK cream followed by photoactivation and repeated for four treatments at intervals of 12-26 days was performed in a small number of minipigs. The applied dose was equivalent to at least five times the maximum clinical dose. Findings were suggestive of effects on the liver, but were inconclusive due to small sample sizes and incomplete evaluation.

According to the Sponsor, although no direct measurement of methyl 5-aminolevulinate in plasma has been performed, measurements of radiolabeled methyl 5-aminolevulinate in pre-clinical studies suggest negligible systemic absorption. Due to a putative instability of the methyl-ALA in serum, traditional pharmacokinetic studies have not been conducted. Instead, photoactive porphyrins (PAP) fluorescence was used to assess the PK of methyl-aminolevulinate HCl in studies PC T101/97 and PC T206/99. According to the Biopharm reviewer, the fluorescence methodology was "not rugged" and not validated. No systemic adverse events were measured and no rationale was provided.

Maximum topical drug exposure data from the clinical trials were not presented in the NDA. The number of tubes used per patient was not presented. Study medication was supplied in 2 g tubes and distribution of study medication to treatment sites (e.g., the Australian study where lesion varied from 1 to 28) was not addressed in the protocol.

However, in the repeated-dose intravenous rat studies, there were decreases in RBC count, hemoglobin, and PCV. In the 7-day IV study, the values were less than control, but appeared to be within normal limits for this species. In the 14-day study, though, those same decreases were again seen with a dose-related trend and according to the Pharm/Tox reviewer appeared to be toxicologically significant.

In the Medical Officer's review (pg. 37) of Levulan, aminolevulinic acid HCl plus PDT, there was some concern regarding a possible treatment-induced decrease in hematocrit. The decrease in hematocrit was small and thought not clinically relevant; however, a Phase 4 safety study was recommended to confirm any treatment-induced decrease. There appeared to be a positive re-challenge in one patient in one of 5 patients.

Between Patient Sterilization of the Device

According to the FDA Microbiologist, instructions for between patient sterilization of the device used in this study were determined to be inadequate and remains unresolved at the time of the written review. According to the User Manual (pg. 11), calibration should be performed with the light measuring diode placed at the lesion surface prior to illumination. There is a concern that lesion preparation might produce an open wound and some bleeding since lesion preparation consists of debriding the AKs with a small dermal curette to remove scales, crusts, and to roughen the surface. Tradename[®] Cream is then applied to the prepared lesion and then covered with an occlusive dressing for 3 hours. The lesion surface area is cleaned with non-sterile saline and non-sterile gauze prior to calibration with the light measuring diode and illumination. Procedures used by individual investigators for between patient sterilization is not known. According to the Sponsor, sterilization instructions were not provided to investigators and there have been no reports of cross-contamination between patients.

The most recent submission from the Sponsor dated June 6, 2002 proposes use of an

The PhotoCure's lamp can be considered a reusable device (RUD).

Long-term safety data

Data from study PC T 202/98, an open exploratory (Phase I/II) study of Tradename Cream 80 mg/g and 160 mg/g applied for 1 or 3 hours in patients with primary AKs, was submitted. Recurrence was assessed at month 12 in all lesions, which had shown complete response in the previous evaluation. It is not clear how lesion identification was ascertained at the 9 or 12-month follow-up. The protocol is silent on this issue.

In the study, only 30 patients were treated with 3h application at 160 mg/g concentration. Of the 30 patients, 29 patients were evaluable for recurrence and 28 patients completed follow-up. The treatment regimen was different in that lesions were treated once or twice (two months following the first treatment) depending on the lesion response after the first treatment.

The primary endpoint was lesion response at 3 or 4 months after the last Tradename treatment (i.e., at month 3 for single-treatment patients, and at 6 months for patients treated twice. Lesions in complete response were evaluated for recurrences after initial treatment.

The overall lesion response rate was 26%; 45% in the 1h 80 gm/g group, 29% in the 1 h 160 mg/g group, 26% in the 3 h 80 mg/g group, and 11% in the 3 h 180 mg/g group. According to the study report, the results of this study revealed high complete response rates, both within patient and on a lesion basis, for all treatment groups. However, Tradename at 3h application 160 mg/g concentration was superior with respect to patient and lesion response rates after only one PDT only; however, there was no vehicle-arm and these data can not be used.

The study results for one patient, Patient 96, considered a complete responder without evidence of recurrence at 12 months needs to be verified. Additionally, there was no post-baseline laboratory data available for this patient. For instance according to Listing 7 (Vol. 1.34, pg. 83), a complete response was recorded for Patient 96 receiving one PDT treatment of 3 lesions. Maximum lesion diameter (mm) for the lesions was 12 mm (lesion 1), 12mm for lesion 2, and 80 for lesion 3. The lamp only illuminates a circular area that is 30 – 55mm (Vol. 1.33, pg. 17). The

protocol did not indicate that 2 lamps were provided and it is uncertain how this patient was treated or if the whether the data listing is in error.

Reviewer's comments:

Study PC T202/98 does not provide adequate long-term safety data needed to evaluate long-term safety. There is no vehicle-arm, the sample size is small (n=30), the treatment regimen and patient population were different, and it is unclear how lesion identification was ascertained at the 9 or 12-month follow-up. The Sponsor was previously advised that it was not clear to the Division whether the long-term efficacy results from Phase 2 Study PC T202/98 could be extrapolated to the Phase 3 studies.

Dermal Safety Studies

Data from 2 dermal safety studies (Study PC T107/0124-Hour Acute (Primary) Irritancy Assay and Study PC T108/01 - 21 Day Cumulative Irritance Assay/With Delayed Challenge) were submitted for review. However, the sensitization study actually was a 9-day cumulative irritancy study with delayed challenge instead of the customary 21-day study and it was conducted in 25 subjects instead of 200 patients usually recommended by the Division. It is not known whether challenge at 21 days might have produced an even higher signal.

Study PC T107/01

Titled: "24-Hour Acute (Primary) Irritancy Assay" (Study Dates April 26, 2001 to April 27, 2001)

This study was a single center double blind, randomized, safety study conducted in 12 healthy male and female patients (4 and 8 respectively) over 18 years of age. The mean age was 61 with a range of 41 – 80 years. Twelve subjects were randomized and tested with Tradename Cream and with the vehicle cream.

The method used was a modification of the Draize acute assay. Six patches (3 with Tradename Cream and 3 with the vehicle cream) were applied to normal healthy skin to the upper back of each subject. One patch in each group was covered with Tegaderm and one with non-breathable occlusive dressing. The creams remained on the skin for 24 hours and all sites were covered with a light occlusive cloth during this period. A six-point dermal response scale was used for each patch after 24 hours.

Results:

Three of the 12 subjects had one vehicle patch with a score of 0.5 (+), i.e., equivocal reaction. No adverse events were reported.

Conclusion

Results of the 24-hour acute irritancy study did not reveal any acute irritation for the 12 subjects tested.

Study PC T108/01

Titled: "21 Day Cumulative Irritance Assay/With Delayed Challenge" (Study dates: June 4, 2001 to July 20, 2001)

(Note: the title of the Study is a misnomer, since this was actually a 9 day cumulative irritancy study with delayed challenge.)

This study was a single center, double blind, randomized, safety study conducted in 25 healthy male and female patients (12 and 13 respectively) over 18 years of age. The mean age was 58 with a range of 32 – 83 years. Twenty-five subjects were randomized and tested with Tradename Cream and with the vehicle cream.

The study was divided into three sequential periods: 1) induction phase where test articles were applied 5 days weekly for 2 weeks, 2) rest phase of 10 days, and 3) Challenge phase where patches were applied to new skin sites for 48 hours. Subjects then returned for dermal score assessment at 48, 72, 96, and 120 hours. An eight-point dermal response scale was used for evaluation of cumulative skin irritation and sensitization.

Protocol Deviations

The following deviations occurred during the study:

- 2 weeks cumulative irritancy assay was performed instead of 21 days. According to the submission (Vol. 1.21, pg. 289), getting any additional information using 21 days was unlikely.
- The inclusion and exclusion criteria actually used were different from the ones defined in the protocol. However, none of the subjects were excluded from the analysis since none fulfilled any of the exclusion criteria.
- An 8-point dermal score was used in the study; instead of the planned 6-point score.

Reviewer's comment:

The protocol deviations appear significant to this reviewer in that the study duration was significantly shortened from 21 days to 9 days of study drug application.

Four patches, two with Tradename Cream and 2 with vehicle cream were applied to normal healthy skin on the upper back of each subject. One patch in each group was covered with Tegaderm. The test articles were applied 5 days weekly for 2 weeks instead of 3 weeks. During the first 9 applications of the induction phase, if any site on a subject's back had a score of 5 or greater, the next patch was to be placed at an adjacent site. If a reaction of 5 or greater occurred at the new site, no further induction applications were to be made; however, the subject was to be included in the challenge phase. A delayed challenge was performed for 48 hours, two weeks after the last cream application in the induction phase. A re-test was performed on 8 subjects about 3 weeks after the challenge phase.

The following 8-point dermal response scoring scale was used:

<u>Score</u>	<u>Description</u>
0 =	No evidence of any effect
1 =	Minimal erythema, barely perceptible
2 =	Define erythema, readily visible; minimal edema or minimal papular response
3 =	Erythema and papules
4 =	Definite edema
5 =	Erythema, edema, and papules
6 =	Vesicular eruption

7 =

Strong reaction beyond test site

Results**Table 24 (Sponsor's Table V, Vol. 1.21, pg. 296): Number of subjects in the Tradename group with each grade of skin reaction after challenge**

Hours	Dermal response score							
	0	1	2	3	4	5	6	7
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
48	15 (60)	5 (20)	3 (12)	0	0	2 (8)	0	0
72	16 (64)	4 (16)	2(8)	1(4)	0	2 (8)	0	0
96	16 (64)	4 (16)				2 (8)	0	0
120	19 (76)	1 (4)				2 (8)	0	0
8 subjects were re-tested								
48	0	5	0	1	0	2	0	0
96	0	0	0	1	0	2	0	0

Eight of 25 subjects did not have any reactions. Cumulative irritancy was noted starting on day 4, with the active greater than the vehicle. Twelve subjects in the Tradename group (includes all subjects in either Tradename or Tradename Tegaderm group) and one in the vehicle group had definite erythema, readily visible; minimal edema or minimal papular reactions recorded on day 4 of cream application.

Of the 25 subjects tested, 10 subjects demonstrated reactions at challenge as follows, 5 subjects (numbers 2, 7, 20, 22, and 23) had minimal erythema and 5 subjects (numbers 5, 8, 9, 17, and 18) demonstrated reaction of definite erythema or erythema, edema, and papules. All 10 subjects were re-challenge 3 weeks after the initial challenge. Of the 10 subjects, 8 subjects were re-challenged three weeks later with one subject (#17) lost to follow-up and no explanation for not re-testing of subject #7 was provided. However, it appears from Table V, Vol. 1.21, page 296 that one subject that had a dermal response score of 1 at 48 hours, reverted to 0 at 72 and 96 hours.

Conclusion

Because the first part of this provocative testing was done only for 9 days, TRADEMARK Cream may be even more irritating and sensitizing (causing skin allergies) than evidenced from this study. A provocative cumulative irritancy and sensitization (allergenicity) study was conducted in 25 healthy adult subjects randomized and tested with TRADEMARK Cream and with vehicle cream. After only 9 days (usually these provocative tests are done over 21 days, but the test was stopped at 9 days), seventeen out of the 25 (68% with an upper 95% confidence boundary of 85%) subjects had definitive erythema and irritation (score greater than 0) with TRADEMARK Cream without occlusion vs. 1 out of 25 with this reaction to the vehicle at the end of the irritation phase.

In the challenge phase 10 subjects showed reactions; however, only 5 out of the 25 subjects (20% with an upper confidence boundary of 40%) had reactions that the Sponsor considered consistent with a topical sensitization (allergic) reaction.

Rechallenge was performed 3 weeks later. Of the 4 subjects considered to have definite reactions, 3 out of 4 re-challenged subjects tested had a positive reaction (75% with an upper 95% confidence boundary of 99%).

Phototoxicity Studies

The Sponsor has requested a waiver of the requirement to conduct phototoxicity studies for Tradename Cream since it is already established by the nature of the active ingredient, methyl aminolevulininate, that all patients treated with Tradename PDT will have a phototoxic reaction at the site of application. The mechanism of action of methyl aminolevulininate involves the build-up of photoactive porphyrins (PAP), which upon illumination results in cell death via the generation of singlet oxygen that destroys vital cellular function.

Reviewer's comments: *The Sponsor is requesting a waiver of requirement of to conduct a phototoxicity study; however, a phototoxicity study has been performed in 34 healthy subjects (ISS, Vol. 1.37, pg. 22). According to the Sponsor, the clinical trial report is not included in the NDA per agreement with the FDA; however; this has not been substantiated. Study 212/00 is a randomized, single center, comparative study of the safety of Tradename-PDT compared to aminolevulininate-PDT (ALA) in healthy subjects. Tradename cream or ALA (20% aminolevulinic acid) cream was applied to a spot on the arm of each subject, 5 hours prior to light therapy (75 J/cm², 180 mW/cm²). Local phototoxic responses were compared before illumination, immediately after illumination, and 24 hours, 72 hours, and 4 weeks after illumination.*

Phototoxicity studies can be waived; however, the potential of photoallergenicity is a clinically relevant as patients will be re-exposed repeatedly as new AKs develop.

Clinical Pharmacology

According to the Biopharm Reviewer, no pharmacokinetic studies have been conducted *per se* due to the putative instability of methyl aminolevulinate HCl in plasma. In the absence of direct measurement of the extent of systemic exposure to methyl ALA after topical application of Tradename Cream, a surrogate marker to assess the PK of methyl ALA, PAP fluorescence, was used. Systemic AEs were not collected during conduct of the Biopharm studies.

E. Summary of Critical Safety Findings and Limitations of Data

Unresolved Safety Issues

Foremost, there is insufficient data available to thoroughly assess safety, The issues are as follows:

- 1) Lack of biochemical and hematologic monitoring data from patients exposed to the proposed repeat dosing regimen of 2 treatment sessions 7 days apart to be able to make a complete and thorough safety assessment. According to Pham/Tox Reviewer, non-clinical data submitted for the first time with the NDA suggests that there may be potential for systemic exposure to ALA after repeated treatments that may result in adverse effects on the liver and blood.
- Additionally according to the Biopharm Reviewer, the Sponsor has not adequately assessed the in vivo bioavailability of methyl-levulinic acid or levulinic acid (the de-esterified form of methyl-levulinic acid).
- No systemic pharmacokinetic data in humans are available. Due to the putative instability of the methyl-ALA in serum, no pharmacokinetic studies have been conducted *per se*. Instead, photoactive porphyrins (PAP) fluorescence was used as surrogate to assess the PK of methyl-aminolevulinate HCl in studies PC T101/97 and PC T206/99.

- The treatment regimen selected by the Sponsor enhances penetration and increases the risk for systemic exposure to Tradename. The risk of systemic exposure is enhanced by: 1) lesion preparation (e.g., removal of crust, scale, etc. with a dermal curette), 2) repeat treatment within 7 days, and 3) use of the highest drug concentration without adequate dose-ranging, and 4) light dose.
 - Laboratory data submitted from 30 patients enrolled in the 3 h, 160 mg/g study arm of an open dose-ranging study was obtained one week after one treatment session. Although no laboratory abnormalities were noted in this small sample, the dosing regimen is different and the small number of subjects studied are insufficient to make a thorough safety assessment. Incomplete laboratory data from patients enrolled in an ongoing basal cell carcinoma study consisted only of scatter plots plotted against baseline at 2 and 7 weeks after the first treatment for serum ALAT, ASAT and bilirubin values. Full data sets were not submitted for review.
- 2) Phase 3 safety database consists of only 130 patients exposed to active drug at the proposed dosing regimen.
- Insufficient numbers of patients have been exposed to the active drug. Minimally, a safety database of 200 patients is needed to determine a 1% incidence of AEs. Only 130 patients have been exposed to one treatment regimen with Tradename Cream-PDT at the proposed dosing regimen in the Phase 3 pivotal studies. There is no applicable re-treatment data and only 3 months follow-up data are available. The amount of drug applied was not documented and presented in the NDA and 63% (65/88) of patients exposed to active drug had less than 4 lesions in one Phase 3 study. Also, the unexpected contact sensitization potential of TRADEMARK Cream is a concern with after only 9 days (usually these provocative tests are done over 21 days, but the test was stopped at 9 days), seventeen out of the 25 (68% with an upper 95% confidence boundary of 85%) subjects had definitive erythema and irritation (score greater than 0) with TRADEMARK Cream without occlusion vs. 1 out of 25 with this reaction to the vehicle at the end of the irritation phase. In the challenge phase, 5 out of the 25 subjects (20% with an upper 95% confidence boundary of 40%) had reactions consistent with a topical sensitization (allergic) reaction. Rechallenge was performed 3 weeks later and 3 out of 4 subjects tested that were considered definite reactors had a positive reaction (75% with an upper 95% confidence boundary of 99%). Because the first part of this provocative testing was done only for 9 days, TRADEMARK Cream may be even more irritating and sensitizing (causing skin allergies) than evidenced from this study. More subjects may have been positive at challenge day 21, thus, the actual potential rate may be understated.
 - The Sponsor acknowledges that the potential to elicit skin sensitization is relevant; however, the Sponsor's contention that in most cases a "single" occasion treatment is expected (ISS, Vol. 1.37, pg. 182) is unrealistic. Typically, actinic keratoses begin to appear in the fourth and fifth decades, and increase in number in the advancing years. Since re-treatment or additional treatment is expected contact sensitization is a concern that should be addressed. Contact sensitization potential was not observed in a similar ALA drug product (Levulan) that does not contain a methyl group. Cross sensitization between the already approved ALA product are unknown. Cross sensitization with endogenous ALA is unknown and is a

concern. Sensitization of the medical personnel administering TRADEMARK Cream is a concern and needs to be addressed by the Sponsor.

- 3) Although considered a device issue, adequate procedures to prevent between cross-contamination with use of the device necessitates that the Sponsor provide an acceptable modification to the use of its device that would allow for adequate patient protection (i.e., Universal Precautions) and at the same time not hinder efficacious use. Procedures used by individual investigators for between patient sterilization is not known. According to the Sponsor, sterilization instructions were not provided to investigators and there have been no reports of cross-contamination between patients. FDA Microbiology Reviewer states that instructions for between patient sterilization of the device used in this study are inadequate. This safety issue remains unresolved at the time of the written review. CDRH will be working to resolve this and approval of the Device should be pending resolution of that safety concern. The final approval of this product, which is only indicated for use with the specific light-emitting device under consideration at CDRH, is pending approval of the use of the device.

A) The Sponsor has proposed

- B) The Division is recommending that a clear covering be used on the diode thereby eliminating  Additionally for horseshoe-positioning device, use of an appropriate disposable cover is also recommended since the placement of the horseshoe-positioning device on intact epidermis cannot be guaranteed in patients with multiple AKs that have been prepared for therapy.

If the Sponsor agrees with the suggestion to use a clear covering to insure non-transfer of infectious material, the Sponsor will need to address the following:

- Demonstrate that the material does not significantly alter light transmittance. This can be done by making measurements using the calibration probe with and without the covering material over the light receptor. The difference in transmission should be easily detected by this method.
- Use animal models to test with the covering material in place for representative lengths of time relevant to clinical use to see if it produces a heat problem that results in formation of a moisture barrier.
- Provide a revised operator manual clearly specifying dosimetry/calibration and treatment with such a barrier in place.
- Discuss/ address the issue of treating multiple AK's in terms of side by side lesions and how to prevent light field overlapping if the lesions are close to each other but can not be treated in a single field.
- Provide a discussion regarding the horseshoe shaped position device in terms of what

its intended use is. Is this for determining distance to insure correct spot size or does it have some function regarding centering of lesion? Is the device designed so that it has an acceptable excess of area to allow sufficient normal skin remaining around the lesion? The diameter of the horseshoe shape opening.

- How the light measuring probe is used (e.g., held by the user during calibration or simply lay on the site).

VIII. Dosing, Regimen, and Administration Issues

It is unclear why there was an upper limit of 6 fields set for the number of treatment field in the Australian study (Study 305/99) and no upper limit nor data collected on the number of treatment fields in the US Study (306/99). According to the Sponsor theoretically 10 treatment fields are possible. There have not been efficacy or safety concerns regarding the number of treatment field per treatment session; however, these data would be useful when selecting a treatment modality for patients and should have been considered. The only one pivotal study, the Australian study, collected treatment field data; however, 89% of the enrolled patients had less than 4 lesion treated.

Each center (pivotal studies 305/99 and 306/99) was provided with two lamps in order that two widely separated lesions could be treated simultaneously. It would be important for treating docs to know that 2 lamps are needed to reduce treatment time for patients with 4 or more lesions. There have been discussions concerning the total length of time per session if illumination time is approximately 10 for each treatment. Total treatment time is of practical importance in patients who have 10 or more lesions since 10 lesions would require at least 50 minutes of irradiation. Add delays of setting up from one lesion to the next could translate into significant delays for irradiation of the last lesions of that patient. According to pre-IND/EP-2 meeting minutes (pg. 6) the Sponsor was encouraged to plan a strategy for cream application when a patient has many lesions to insure that no lesion is treated outside of the time window. However, pivotal Phase 3 protocols contained no such recommendations and no data are available for labeling.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation Vehicle-controlled Studies

Female patients tended to report more local adverse events than the males in the same treatment group. A between gender difference of $\geq 10\%$ for skin pain, stinging skin, crusting, blisters, and pruritus was noted. There was a difference noted between female patients with non-local adverse events (Vol. 1.37, Table 81, pg. 162) in active and vehicle groups (17 (35%) female patients in the Tradename Cream group vs. 3 (14%) females in the vehicle group). No details were provided and the numbers are small.

Overall Tradename Cream Experience (AK and BCC)

For overall Tradename experience (AK and BCC), the Sponsor concluded that the number of adverse events were similar in male and female patients on active drug.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Evaluation of Evidence Age (safety)

Vehicle-controlled Studies

A total of 229 patients comprised the safety population in placebo controlled studies for the actinic keratosis indication. Of the 229 patients enrolled, 149 patients were in the Tradename Cream study arm. Eighty (54%) of the patients receiving Tradename Cream were ≥ 65 years of age.

According to the Sponsor's analysis for local adverse events reported by ≥ 1 % of all patients in vehicle-controlled AK studies, there is a $\geq 10\%$ between age group difference for peeling skin, bleeding skin, and itching as compared to patients ≤ 65 years of age. There also was a tendency towards severe skin pain. . No difference was noted in efficacy between patients that were younger than 65 years and those 65 years and older.

Overall Tradename Cream Experience (AK and BCC)

The Sponsor presented the incidence of adverse events in AK and BCC studies by patient age group in the safety population (Vol. 1.37, pg. 158 & 159). According to the submission, a total of 753 patients were treated, with 560 (74%) patients with adverse events. Of the 560 patients a total of 354 (73%) reported local AEs and 95 (20%) reported non-local AEs.

The Sponsor concluded that generally, the results were similar for both age groups except that there was a $\geq 10\%$ difference in erythema in patients with BCC (57% in patients < 65 and 47% in patients > 65 years of age. The results suggest that the profile of local and non-local adverse events did not differ between < 65 years and ≥ 65 years of age.

Evaluation of Evidence for Race or Ethnicity Effects

All patients in the vehicle controlled studies were Caucasian. Of these the number of patients with skin Type III or higher was low (N=19). The incidence of local adverse events appears to have been higher in patients with skin Type III or higher for at least one reported AE. Burning sensation was higher in skin Type III (20 or 65%) vs. 23 (33%) reported for skin Type II. This difference was unexpected and according to the Sponsor may have been caused by the low numbers of patients studies with skin Type III or higher than with other skin types. The incidences of non-local AEs for patients treated with Tradename Cream were similar for all skin types studies.

C. Evaluation of Pediatric Program

The Sponsor is requesting a waiver of requirements to assess the effects of Tradename Cream for treatment of pediatric patients 16 years and younger. The rationale provided is that actinic keratosis occurs very rarely in the pediatric population. The estimated occurrence of the disease in children in the US is unknown but is considered rare (less than 1 in 10,000). This waiver request appears reasonable.

D. Comments on Data Available or Needed in Other Populations

All patients in the Phase 3 actinic keratosis studies were Caucasian; therefore, there is no information concerning the safety profile of Tradename-PDT treatment in other ethnic groups (e.g., Hispanics, Asians) who are at lower risk, but not zero risk, for development of actinic keratoses.

X. Conclusions and Recommendations

A. Conclusions

Efficacy has been demonstrated in two clinical trials with use of two treatment sessions of Tradename Cream-PDT over vehicle cream-PDT in treatment of actinic keratosis of the face and scalp when used as supplementary to curettage. From a clinical perspective, the application is **Approvable**; however, there are multiple concerns that are either unresolved or were not adequately addressed by the Sponsor in the submitted dataset.

The quality and quantity of the safety database submitted with the NDA application does not include enough information to exclude possible safety issues for the proposed dosing regimen. New data submitted for the first time at NDA submission and new information resulting from queries made by the Division during NDA review has made it evident that additional safety data is needed prior to approval while other informational needs can be derived from Phase 4 studies.

It is determined that the Trademark cream may be used safely with restrictions/precautions placed in labeling if the Sponsor adequately addresses the following prior to approval:

- 1) The Sponsor needs to conduct an adequate 21-day contact sensitization potential study of methyl-ALA and in the challenge phase test both ALA which is an endogenous metabolite (to rule out cross-sensitization) and methyl-ALA.
- 2) Provide data driven instruction for prevention of sensitization of healthcare professionals handling Trademark cream.
- 3) As part of labeling develop visual instructional material (e.g., video, CD, etc.) to ensure optimal safety and efficacy with use of the drug-device. The material should not be promotional in nature and submitted to the Agency for approval prior to distribution. The instructional material should include (but not limited to) dosage and administration procedures, and Adequate procedures to prevent cross contamination with between patient use of the device are also needed.
- 4) Provide the following information relative to labeling:
 - A. Identify types of gloves for which methyl-ALA and excipients found in TRADEMARK Cream will not penetrate.
 - B. Submit the line listings and serum transaminase level information for the patients treated with TRADEMARK Cream in the BCC study(ies).
 - C. Describe lack of safety monitoring done in Phase 3 studies to preclude systemic adverse events as suggested in preclinical studies.
 - D. Provide the maximum duration of time permissible between application and illumination. Please provide information regarding needed adjustments to duration of light treatment following inadvertent prolonged exposure to TRADEMARK Cream before light exposure. Provide information regarding what a patient should do if there is prolonged exposure without subsequent light treatment - e.g. avoidance of sunlight for # days. All of these pieces of information should be supported with data and not hypothetically derived. As the disposition of methyl-ALA inside the body is not clearly known, please clarify the issue and provide supportive documentation.
 - E. It is unknown whether the risk of illumination after longer application periods (e.g., up to _____ with TRADEMARK Cream is warranted for the treatment

- of actinic keratosis. It is recommended that the cream should be rinsed off and illumination should be avoided. Labeling should be adjusted accordingly.
- F. Provide instructions for what should be done with light overexposure - e.g. would management be similar to care for burns from other causes?
 - G. It is suggested that the Sponsor submit a Patient Package Insert to describe to patients the PDT procedure.
 - H. Provide information regarding the radiant heat and temperature achieved with skin surfaces exposed to the Curelight Model 01 device.
 - I. Provide information and rationale regarding how long the redness and swelling last before the patient should contact their doctor. This should be supported with data from studies.
 - J. Inform as to how long it takes for the surrounding skin reddening, swelling, crusting, blistering, edema, ulceration, peeling, itching and bleeding to resolve. Again, this should be supported with data.
 - K. Give actual percentages of patients with peeling, bleeding, itching and severe pain in patients aged 65 and older (being greater than that in younger patients).
 - L. Provide the number of patients treated with TRADEMARK Cream - the denominator for adverse events should not be diluted with vehicle or other treatments.
 - M. Calculate the percentages for adverse reactions based on occurrence(s) per patient. Also, please provide the upper 95% confidence interval.
 - N. Provide information regarding severity of burning sensation and skin pain seen in U.S. and Australian studies.
 - O. Identify the light transmittance through 1 millimeter of TRADEMARK Cream at 30^N C.
 - P. Please provide a list of anesthetics and the frequency with which they were used in Phase 3 studies.
 - Q. Identify the type of spatula used in clinical studies (e.g. what is the composition?).
 - R. Provide subgroup analysis with regard to wait time or information regarding compensatory calculations for lamp exposure during Curelight 01 light treatment.
 - S. Adequate procedures to prevent cross-contamination with use of the device necessitates that the Sponsor provide a modification that is acceptable to the Agency for use of the device (Curelight 01 lamp) that would allow for adequate patient protection (i.e., Universal Precautions) and at the same time not hinder efficacious use.
 - T. Please provide information/description for treatment of multiple lesions - e.g., multiple lamps vs. single lamp, staggering of lesions, etc.
 - U. Provide information regarding effect of local anesthesia and increased pain intolerance on adverse events (i.e., were patients who were given local anesthesia more likely to have burns due to failure to feel discomfort and/or were they less likely to report local adverse events such as pain and stinging?).
 - V. Provide information regarding what should be done with the lesion area after exposure to red light treatment with the Curelight 01 lamp.
 - W. A visual aid should be submitted which would be part of labeling. The treatment

process appears to be fairly complicated and such an aid should allow for safer (for both practitioner and patient) and more efficacious use of your drug/device).

- X. Information on light and drug overdosage needs to be symmetrical and supported by data.
- Y. Identify if _____ is appropriate to be placed under _____

- 5) The Sponsor should submit the clinical trial results of Study PC T212/00 which is a Phase 2 randomized, comparative phototoxicity study of Trademark cream vs. ALA 20% cream applied for 5 hours conducted in healthy individuals. Sponsor should submit a complete safety update including all safety data from other studies conducted with Trademark cream should be submitted.
- 6) Commit to conduct Phase 4 post-marketing studies. The Phase 4 post-marketing studies are listed below.
- Sponsor should agree, as a Phase 4 commitment, to conduct a 12-month study in at least 200 evaluable patients with 10 or more lesions (located on the face and scalp) have the following collected: hepatic transaminases (ALT and AST), alkaline phosphatase, total bilirubin, and complete blood count plus differential data at baseline and at one week after the second repeat dose 7-day regimen.
 - The Sponsor should agree to conduct a longer-term Phase 4 study documenting the effects of multiple retreatments and recurrence rate with its product. Actinic keratoses may be considered to be a chronic remittent disease and multiple retreatments are common, especially in older, sun overexposed patients.
 - The Sponsor should agree to conduct a Phase 4 study to determine the photoallergenicity potential of TRADEMARK Cream with a diluted form of TRADEMARK Cream.
 - The Sponsor should agree to conduct a safety and efficacy Phase 4 study of Metvix in patients of Asian or Hispanic heritage.
 - The Sponsor should agree to conduct additional Phase 4 studies as per the Pharm/Tox reviewer and Biopharm reviewer should also be agreed to by the Sponsor.
- 7) The following are informational needs that were forwarded to the Sponsor and are still outstanding. During conduct of the Phase 3 studies:
- Was there any patient discomfort associated with lesion preparation?
 - Did the investigators use anesthetics prior to lesion preparation?
 - Did or should investigators use gloves during Metvix cream application?
 - Is there any personnel protection instructions for inadvertent exposure to Metvix cream?
 - Is Tegaderm® transparent or translucent, and what instructions were given to patients regarding restrictions during the 3-hour interval between Metvix application and removal?
 - Did patients experience any AEs (e.g., burning, stinging, itching, etc.) during Metvix application prior to removal? If so, what was the remedy?
 - What instructions were provided regarding use of 2 lamps? Was there a strategy developed for cream removal, avoidance of overlapping treatment fields, etc.? Should there be a limit to the number and location of treatment fields?
 - What was the purpose for use of water spray and fan during illumination? Was this technique included in the protocol? What type of water spray was used and would use of a water spray disperse residual Metvix cream?

- I. Since the Sponsor did not provide disinfection/sterilization procedures, what techniques were employed by the investigators for between patient use of the device?
- J. Did the study nurse follow a triage protocol for referral to the sub-investigator for treatment of local adverse events?
- K. Who recorded local and systemic AEs at the following:
- before and after each treatment session,
 - at 2 week post-treatment visit, and
 - 3-month efficacy endpoint visit?
- L. Were there post-treatment instructions provided for patients (e.g., restrictions immediately after treatment, remedies for possible AEs such as swelling, burning, crusting, etc.).

Labeling Recommendations

ITEM 2A
DRAFT PACKAGE INSERT FOR TRADEMARK®
(METHYL AMINOLEVULINATE)

Sponsor:

PhotoCure ASA
Hoffsveien 48
N-0377 Oslo Norway

Sponsor's Authorized US Agent:

Clementi & Associates
919 Conestoga Road
Rosemont, PA 19010
USA

Date of Document: 20 September 2001
Revised July 25, 2002

14 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

/s/

Brenda Vaughan
9/6/02 09:31:44 AM
MEDICAL OFFICER

Markham Luke
9/6/02 10:11:27 AM
MEDICAL OFFICER

Approvable recommendation for methyl ALA 16.8% Cream for use
with Curelight Lamp, when used as supplementary or
ancillary to curretage as treatment for AK. See
also Clinical TL Addendum to MOR. Metvix trademark
found to be unacceptable.

Jonathan Wilkin
9/12/02 06:09:06 PM
MEDICAL OFFICER
See TL summary memorandum entered into DFS on 912/02