

Executive Summary

PhotoCure has prepared this briefing document to facilitate review of the data that support the effectiveness and safety of methyl aminolevulinate (MAL) photodynamic therapy (PDT) in the treatment of superficial and nodular basal cell carcinoma, BCC. MAL-PDT consists of application of cream containing methyl aminolevulinate followed by illumination. This NDA is for a drug device combination.

Based on prior discussion with the Division of Dental and Dermatologic Drug Products, PhotoCure believes we are in general agreement on key issues to address in our Briefing Document. Historically, applications for market approval provided evidence in key disciplines such as clinical pharmacology, pharmacokinetics and toxicology. PhotoCure has conducted such studies, which are wholly described in the body of Briefing Document. This summary is intended 1) to demonstrate easily that key questions for proper clinical use have been addressed, and 2) to provide the reviewer with a quick reference guide to important studies. We look forward to a productive discussion regarding the use of MAL-PDT in the treatment of basal cell carcinoma (BCC).

Introductory Statement

Photodynamic therapy has been used in dermatology for many years. Most of the literature published has been from European sources until the recent (December 1999) approval of Levulan[®] Kerastick[™] (aminolevulinic acid HCl) for actinic keratosis (AK) in United States. PhotoCure ASA (which grew from the research at the Norwegian Radium Hospital, NRH, Oslo, Norway) began to accumulate experience with MAL PDT through the active research program at the NRH. (The patients referred to in the compassionate use study PC T001/97 were those studied as part of the NRH program and before major regulatory filings occurred.) Therefore, PhotoCure began its clinical research efforts with prior experience in hand. The first application for marketing authorization was approved in Sweden in 2002, and currently, 15 European countries, Australia and New Zealand have approved the product. It is being marketed in Denmark, Finland, Germany, New Zealand, Norway, Sweden and UK. In all European countries and in New Zealand, the product is approved for treatment of actinic keratoses on the face and scalp and for treatment of basal cell carcinoma unsuitable for other available therapies. In Australia, the product is approved for treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses on the face and scalp when other registered therapies are unacceptable and primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate.

What were the goals of PhotoCure's Clinical Development Program?

As stated in several review articles published in peer-reviewed journals, the goals of treatment of nodular and superficial Basal Cell Carcinoma includes: **tumor removal, tissue preservation** and **cosmesis**. In the placebo-controlled studies, **tumor removal** is achieved, and in these and the supportive studies the low incidence of recurrent tumors

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supports complete tumor removal in the majority of patients treated under clinical study conditions.

Data pertaining to **tissue preservation** and **cosmesis** has been collected in Phase II and III studies. (PC T205/98, PC T307/00, PC T308/00, PC T303/99, PC T304/99, and PC T310/00). In two of these studies (303/99 and 304/99) superior cosmesis was shown compared to surgery and cryotherapy.

Clinical Pharmacology

Did PhotoCure conduct adequate studies to permit quantitative aspects of the proposed treatment to be properly described in "Instructions for Use" for practicing dermatologists?

Yes, PhotoCure conducted several studies to define light and cream dose (including build up and photobleaching of fluorescence, cream concentration and application time, and light dose) using a widely accepted surrogate marker of the photosensitizer, photoactive porphyrin (PAP). Not all possible combinations could be studied practically, so PhotoCure selected several likely and patient accommodating combinations for study. This included the currently recommend 3 hour cream application and a light exposure using non-coherent light of wavelength 570-670 nm and a total fluence of 75 J/cm².

- PAP fluorescence has been used as a logical surrogate to assess the pharmacokinetics of methyl aminolevulinate following application of MAL Cream and to describe the accumulation of PAPs in BCC and actinic keratosis (AK) lesions and surrounding skin to which cream was applied.
- Absorption and penetration depth in most BCC lesions achieved a plateau within a few hours.
- There was clear evidence of specific localization in lesions relative to surrounding normal skin.
- Studies PC T101/97, PC T203/98 and PC T206/98 show that a MAL cream concentration of 168 mg/g and an application time of between 3 and 10 hours are optimal

Clinical Efficacy

Are there two adequate and well-controlled trials to support the efficacy of MAL-BCC in the treatment of BCC?

Yes, PhotoCure has conducted 2 placebo controlled in 132 patients with histologically confirmed nodular BCC (PC T307/00 and PC T308/00). Study PC T307/00 was conducted in the United States and PC T308/00 in Australia. Both studies demonstrated superiority to placebo (including lesion preparation). In addition to these 2 studies, the Phase III program also included the following studies:

- One open, randomized, controlled trial with simple surgical excision as comparator in patients with low risk nodular lesions (PC T303/99). The study showed non-inferiority to surgery with respect to response rate and superior tissue conservation and cosmetic outcome.
- One open, randomized, controlled trial with cryotherapy as comparator in patients with low risk superficial lesions (PC T304/99). The study showed non-inferiority to cryosurgery with respect to response rate and superior tissue conservation and cosmetic outcome.
- Two uncontrolled studies in high-risk patients unsuitable for conventional therapy (PC T205/98 and PC T310/00). The studies demonstrated a high success rate in a majority of the patients and excellent cosmetic outcome without disfigurement.

In the current therapeutic 'tree' for the treatment of BCC what is the role of non-surgical treatment?

Comparison to Existing Treatment Modalities:

Excision surgery, Mohs' surgery, and cryotherapy and electro-desiccation with curettage have not been the subject of adequate and well-controlled trials, although this notion has been quoted in major reviews. The meta-analyses performed in several reviews do not represent the true risk associated with surgical therapy, nor the true benefit. PhotoCure believes that MAL-PDT is not intended to replace other modalities but to complement them. However, MAL-PDT has demonstrated its efficacy (superior to placebo and non-inferior to surgery and cryotherapy) and superior tissue conservation and cosmesis in prospective, multi-center studies in nodular and superficial low-risk BCC lesions. MAL-PDT seems well suited for these lesions.

Overall Safety

Adverse events have been categorized as local and non-local. Since systemic absorption is very low, the clinical significance of changes in systemic safety parameters is of low relevance—nonetheless they are reported. The total number of patients exposed is 546 in BCC studies, 394 in AK studies, totaling 940 patients exposed to MAL-PDT. The most common complaints were erythema, pain skin, and burning sensation skin. All these were expected phototoxic reactions and were transient and mostly mild..

Other Key Safety Findings:

Non-local (systemic) adverse events: Compared to both placebo, surgery and cryotherapy, a similar and low number of possible systemic adverse events were reported.

Liver toxicity: The liver function tests results recorded at baseline and after treatment in three studies were randomly distributed with no indication of a dose-response relationship and no increases reaching 100% or twice the upper limit of normal. It is concluded that there is no evidence of a hepatotoxic effect of PDT with topical MAL Cream.

- Skin Sensitization and Local Irritation: A 21 days sensitization potential study in 156 healthy volunteers (PC T110/03) shows that methyl aminolevulinate cream can induce sensitization in over half those exposed to extreme conditions – three weeks continuous application - but that there is no cross-sensitization to the endogenous ALA. Methyl aminolevulinate Cream has been on the market for close to 2 years and around 25,000 MAL-PDTs have been performed. Only one instance of sensitization towards methyl aminolevulinate cream has been spontaneously reported. In controlled clinical studies in over 900 patients none of the AE reported was suspected to reflect contact sensitization. Sensitization does not seem to be a clinically significant problem. Health care providers are instructed to use medical gloves and to apply the cream using a spatula.

Safety – Postmarketing: The data described in the post-marketing reports are consistent with the general pattern of AEs observed in clinical studies. The data support the conclusion that methyl aminolevulinate cream 168 mg/g-PDT is safe and well tolerated when used in the treatment of BCC and AK.

Conclusions:

The MAL-PDT program shows efficacy greater than placebo in two well-controlled trials. The dosing used is patient accommodating as it permits complete office treatment. MAL-PDT has also shown clear medical benefit over both surgery and cryotherapy in two prospective multicentre studies. The safety profile has been well examined. Contact sensitization has been seen under extreme conditions but has not been seen in the clinical program. MAL-PDT has been shown effective even in large lesions unsuitable for other treatment and retains acceptable efficacy and good cosmetic outcome. MAL-PDT meets the 3 goals of treatment of nodular and superficial BCC, namely **tumor removal, tissue preservation and cosmesis.**