BRIEFING DOCUMENT FOR FDA ADVISORY COMMITTEE MEETING FOR PHOTODYNAMIC THERAPY WITH METHYL AMINOLEVULINATE CREAM FOR TREATMENT OF BASAL CELL CARCINOMA NDA 21-576

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ABBREVIATIONS

AE	adverse event
AK	actinic keratosis
ALA	5-aminolevulinic acid
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical (classification of drugs)
BCC	basal cell carcinoma
cm	centimeter
CR	complete response
CRF	case report form
eval	evaluation
FDA	Food and Drug Administration
FU	fluorouracil
g	gram
h	hour
ISS	integrated summary of safety
ITT	intent-to-treat
IV	intravenous
J	Joules
m	month
MAL	methyl aminolevulinate
mg	milligram
mW	milliwatt
NDA	New Drug Application
nm	nanometer
NOS	not otherwise specified
PAP	photoactive porphyrins
PDT	photodynamic therapy
PpIX	Protoporphyrin IX
PR	partial response

ABBREVIATIONS

PMA	premarket approval
SAE	serious adverse event
SD	standard deviation
UK	United Kingdom
US	United States of America
WHO	World Health Organization

1 INTRODUCTION

1.1 PhotoCure ASA

PhotoCure ASA (PhotoCure) is a pharmaceutical company founded in 1993 by the research foundation at the Norwegian Radium Hospital (NRH) in Oslo. The NRH is the leading cancer hospital in Norway and among the largest in Europe. Basic and clinical research in photobiology has been one of the major research areas at the hospital for the last 20 years. The company develops and markets pharmaceuticals and medical devices for the diagnosis and treatment of cancer and other diseases, using its proprietary photodynamic therapy (PDT) technologies established at NRH. PhotoCure has an important and long-standing research relationship with the Norwegian Radium Hospital Research Foundation. In addition, PhotoCure has ongoing research collaboration with a number of other academic institutions.

1.2 Photodynamic Therapy and Detection for Cancer Diagnosis and Treatment

Photodynamic action involves the activation of a photosensitizer by light. Subsequent energy and electron transfer from the photosensitizing molecules to oxygen induces the formation of reactive oxygen species, which themselves are responsible for cytotoxic reactions. The principle of photodynamic therapy (PDT) is not new in the sense that the ability of certain dyes to sensitize microorganisms for their destruction by a following exposure to light was first mentioned in 1900. For optimization and standardization of PDT, various photosensitizing substances, especially porphyrins have been studied. In 1924, it was observed that hematoporphyrin caused a bright red fluorescence in tumor tissues when illuminated with UV light. Topically applied substances have received increasing interest because they avoid the generalized photosensitization observed with systemically administered photosensitizers. Lately, increasing interest has developed for using precursors of endogenous photosensitizers. Especially, large amounts of preclinical and clinical work have been published on the use of 5-aminolevulinic acid (5-ALA or ALA). ALA is the precursor of porphyrins in the metabolic pathway of heme synthesis. Exogenous application of ALA leads to increased intracellular production of photoactive porphyrins (PAP), such as protoporphyrin IX. Illumination by light with proper wavelength leads to photoactivation of PAP and cell death.[1]

Recently, it has been shown that derivatives of ALA have important biological properties that are different from ALA and that provide them with unique possibilities for use in diagnosis and treatment of cancer. PhotoCure has now developed medicinal products based on methyl and hexyl esters of ALA, methyl aminolevulinate (MAL) and hexyl aminolevulinate (HAL) respectively. A cream containing MAL together with a light source has been developed for treatment (MAL-PDT) of actinic keratosis (AK) (Figure 1) and basal cell carcinoma (BCC), and a solution of HAL (Hexvix®) for instillation in the bladder before cystoscopy is in advanced clinical development for improved detection of bladder cancer.

Figure 1: Efficacy of MAL-PDT in Extensive and Severe Actinic Keratosis

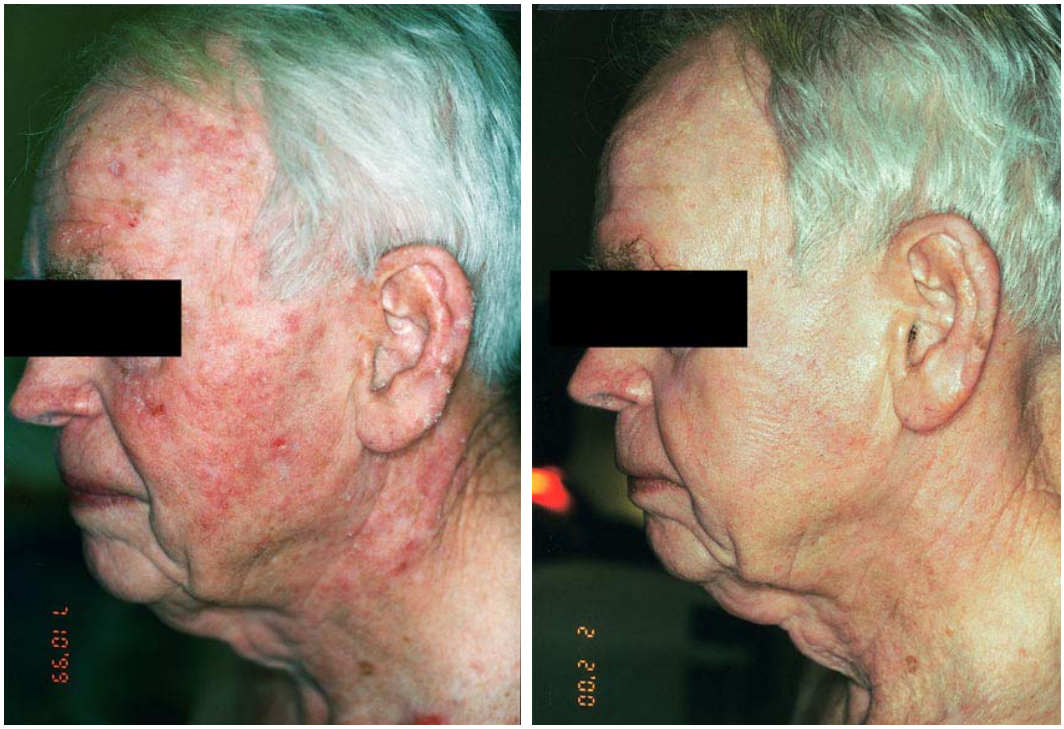


Figure 1: Efficacy of MAL-PDT in extensive and severe actinic keratosis (AK) (sun-damaged skin).

2 PROBLEM STATEMENT

2.1 Basal Cell Carcinoma (BCC)

Non-melanoma skin cancers (NMSCs) constitute more than one-third of all cancers in the United States. The most frequent type of NMSC is BCC and, in fair-skinned people, BCC of the skin is the most common malignant tumor of any organ.[2] Estimated age-adjusted incidence figures per 100,000 of the white population in the United States range from 407 to 485 in men and from 212 to 253 in women.[2,3] The number of cases of BCC diagnosed and treated in the United States was estimated at 1,200,000 in 1995.[4] In Australia, the incidence is as high as 1000 to 2000 per 100,000 population[2] and in Western Europe the incidence is approximately 200 per 100,000.[5]

The incidence of BCC and other NMSCs is increasing rapidly, as exemplified in the United Kingdom (UK), where it has increased 238% over 14 years.[6] In white populations in Europe, the United States, Canada, and Australia, the average increase of NMSC was 3% to 8% per year over the past 4 decades. The rising incidence of NMSC is probably due to a combination of increased sun exposure or exposure to ultraviolet light due to ozone depletion, increased outdoor activities, and changes in style of clothing. Over 80% of BCCs occur on areas of the body that are frequently exposed to sunlight, namely the head, particularly forehead, nose, cheek, ear and orbit, the neck, and back of the hands.[7] Sun exposure that occurs prior to an age of 20 years is particularly important, and tumors typically occur between 40 and 60 years after the damage was sustained.[4,8,9] The increase in life expectancy also undoubtedly has contributed since the incidence rises with age. Thus in 1998, the incidence of BCC in individuals over 75 years old was approximately 5 times higher than that of individuals between 50 and 55 years old.[10] There is an increased risk of NMSC in white populations, especially those with blue eyes, a fair complexion, skin type I and II (sunburn easily, suntan poorly, freckle with sun exposure), and red or blond hair. NMSC is uncommon in black populations, Asians, and Hispanics.[9,11]

The majority of BCCs arise on the head and neck where tissue preserving treatment modalities and cosmesis are important for obtaining a successful treatment results.[12,13,14] Based on their morphology and histology, most tumors are categorized as nodular, superficial, or morpheaform. In most studies, 45% to 60% are nodular, frequently with ulceration, 15% to 35% are superficial and the remainder are morpheaform, infiltrating or pigmented.[14,15] Histologically, tumor cells resemble those of the basal layer of the epidermis. Mitotic figures may be frequent, despite a usually slow growth rate attributable to a high rate of apoptosis.

BCCs are rarely metastatic and normally run a slowly progressive course of peripheral extension but they have considerable capacity for causing local destruction. In susceptible individuals, tumors are often multiple and new lesions arise over time.[16] Metatypical and morpheaform BCCs are more likely to demonstrate pronounced invasive growth. These aggressive subtypes are associated with high risk of recurrence and morbidity. On the other hand, both nodular and superficial BCCs often exhibit noninfiltrative or superficial

growth patterns. These non-aggressive subtypes are generally associated with lower risk as compared with infiltrative and morpheaform BCCs. However, other tumor characteristics, such as size and location may also render these BCCs difficult to treat successfully.

2.2 Clinical Factors Relevant to Treatment Options

There are numerous clinical factors that determine the options for treatment, including the nature of the tumor (primary or recurrent), tumor type, and its location, size, borders, and growth rate.

Overall, it has long been recognized that certain BCC lesions have a high risk of recurrence after conventional treatment.[16,17,18,19] For instance, some anatomic sites are more prone to recurrence or even development of metastatic disease, because complete tumor removal is more difficult to achieve.[20] High-risk BCC lesions may have one or more of the following characteristics:

- Long duration or neglected;
- Located in adverse anatomic sites, in particular mid-face or ear;
- Recurrent or inadequately treated;
- Large tumors, particularly those greater than 20 mm in diameter;
- Aggressive histological subtype; and/or
- History of radiation exposure.

Tumors of the mid-face, including the nose, periocular and perioral areas, ears (the so-called “H-zone”), scalp, and forehead have the highest risk of recurrence.[17] Larger tumors, particularly those which show histological signs of infiltration, sclerosis, and multifocality, which tend to occur in areas of sun-damaged skin, are also likely to recur more frequently as compared with non-infiltrating, unifocal nodular and superficial lesions. A history of recurrence is also a predisposing factor to further recurrence. Lesions occurring in patients with multiple lesions also have an increased tendency to recur.[18,19] Based on these characteristics for high-risk BCC, the BCC population can be divided into high-risk and low-risk BCC subpopulations, where low-risk BCC are those superficial and nodular lesions that lack the features of high-risk BCC.[20]

Unfortunately, there are no standardized methods for reporting cure and recurrence rates of BCC and there is a serious lack of prospective comparative studies.[15,20,21] Many series are small, single-center, retrospective, and subject to selection bias. Estimates of the recurrence rate for primary BCC after treatment vary greatly (1% to 39%).[15, 22] Despite these limitations, it is clear that 5-year recurrence rates of high-risk lesions treated with conventional methods are much higher than those of low-risk lesions.[17]

The main goals in treatment of BCC lesions are to remove the tumor, conserve as much healthy tissue as possible, preserve tissue function, and avoid disfigurement.[20] Several

surgical procedures are used in the treatment of BCC lesions. Mohs surgery is a specific surgical treatment procedure that has been implemented in the treatment of a subpopulation of (high-risk) BCC lesions. Certain lesion sites (especially the "H-zone") and lesions of large size may exhibit high risk for subsequent morbidity in regard to disfigurement and reduced functionality.

2.3 The Need for New Treatments

The goals of treatment of BCC are to prevent further local invasion and destruction by achieving a cure, while maximizing tissue conservation, thereby minimizing disfigurement and avoiding interference with function of critical structures such as the nose, eyelids, mouth, and orbit.[20] Guidelines for care are provided by the American Academy of Dermatology[23], the National Cancer Institute[24], and the British Association of Dermatologists.[25] However, a recent review of evidence-based treatment options and outcomes stresses the lack of large prospective studies and the paucity of studies comparing 2 treatment modalities.[15,20,21,26] Current treatments represent a compromise between ensuring a cure and obtaining an acceptable cosmetic result. A variety of surgical and non-surgical therapeutic modalities are available for BCC, but cosmetic results are frequently highly unsatisfactory. Thus, new treatment modalities with comparable efficacy to existing methods, which offer better tissue conservation, and result in low treatment-related morbidity and good cosmetic outcome, are desired.

The choice of treatment modality, which determines the response rate, incidence of recurrence, and cosmetic outcome, depends on the tumor type, histology, definition of margins, size, and site, whether it is primary or recurrent, and also on the expertise of the physician or surgeon. Patient variables such as age, medical status, psychological factors, and concomitant medications should also be taken into account. Surgical excision with primary closure, local flap, or skin graft if required, is the most frequently performed treatment for nodular lesions. Many favor cryotherapy, in particular for superficial lesions. Curettage with or without cauterization of the margins is also frequently used. Radiotherapy is effective, but generally reserved for elderly patients with large lesions who are unsuitable candidates for major surgery and anesthesia. Local cytotoxic agents such as 5-fluorouracil are also used for treatment of superficial lesions but treatment is highly irritant to the skin and recurrence rates are high. Interferon can be effective but it is inconvenient due to the requirement for multiple injections at multiple visits, as well as a high frequency of local and systemic adverse effects.

Although the results of excision surgery for nodular lesions are believed to be good in terms of cure rate, the cosmetic outcome is frequently far from satisfactory with a surgical scar, often in cosmetically sensitive areas. In addition many patients do not like subjecting themselves even to minor surgery. While the prognosis of superficial lesions is generally good, cosmetic results of cryotherapy or surgery are not less problematic than for nodular BCC. These lesions frequently contain islands of papular growth and are bounded by a slightly raised thread-like margin, which is irregular, and may be deficient making delineation of the edge difficult. A wide area of excision is therefore required to minimize the chance of leaving residual tumor. Mixed nodular/superficial lesions share features of both types and present the same difficulties for treatment.

Choice of treatment for high-risk BCC lesions that are not suitable for conventional therapy depends on the type, size, depth, and location of the lesion, together with the skills of the healthcare personnel and resources available to them. The trade-off between eradication on the one hand and cosmetic outcome with preservation of functionality on the other is even more critical than for low-risk lesions. However, the treatment options available are far fewer than for superficial and nodular low-risk lesions. Cryotherapy and electrodesiccation with curettage are not recommended; they are unsuitable for large tumors and incomplete removal of tumor with recurrence is common.[27] Cosmetic results are also frequently unacceptable for all but the smallest tumors, with scarring that is easily seen on sun-damaged skin.[28]

Recurrence rates after surgery of high-risk lesions vary but are dependent on adequate removal of the tumor, which must be histologically controlled. Visual estimation of a margin of 3 to 5 mm is frequently inaccurate with tumor extending beyond the clinically apparent margins. Difficulties in delineation of the lesion caused by scarring further complicate the treatment of recurrent lesions. To prevent recurrence, sacrifice of normal tissue is often substantial with larger margins of 10 mm or more recommended for some lesions. Primary closure may be possible, but healing by second intention with or without subsequent grafting is sometimes the only management option. Scarring may lead to functional disability. Approximately 8% of surgical scars are complicated by the occurrence of keloid or hypertrophy.[29]

Radiation is a useful treatment modality with good cure rates for high-risk lesions either alone or as an adjunct to surgery. However, it is time-consuming and expensive and can lead to complications such as posttreatment fibrosis, chondritis, tissue necrosis, and wound breakdown. Risk of carcinogenesis and radiation dermatitis makes the therapy unsuitable for younger patients. To obtain the best cosmetic results, fractionation is recommended, but multiple treatment sessions are often very inconvenient for elderly patients.

Mohs micrographic surgery[27,30] is probably the optimum form of treatment for recurrent and other forms of BCC with high risk of recurrence. In this procedure, sections of marked, anatomically orientated segments of tissue from the entire periphery of the excision specimen are examined microscopically, with or without immuno-histochemical staining. This provides maximum assurance of tumor clearance with minimal loss of surrounding normal tissue. However, Mohs surgery is very time-consuming and expensive and requires highly specialized staff. Excision and reconstruction of large BCCs may require the additional services of histopathologists, as well as plastic, oculoplastic, or head and neck surgeons.[27] This imposes serious constraints on its general applicability.

Therefore, novel treatment options are required for treatment of both low-risk and high-risk BCC. They should have the following characteristics:

- Comparable (or superior) response and recurrence rates to those of the best current treatments;
- Maximum preservation of healthy tissue with good cosmetic and functional outcome;

- Low treatment-related morbidity;
- For high-risk lesions, more readily and widely applicable than Mohs surgery;
- No significant systemic adverse reactions.

2.4 Photodynamic Therapy with MAL PDT

For PDT to be an effective and well-tolerated treatment for BCC, it should meet the above requirements and have the following additional features:

- No or minimal toxicity other than that associated with the photodynamic response to illumination;
- Distribution and pharmacokinetic characteristics that favor selectivity for tumor over normal tissue;
- Rapid clearance after treatment to avoid generalized photosensitivity;
- High triplet quantum yield and efficient energy transfer to generate singlet oxygen;
- Strong absorption of light by the photosensitizer in the red part of the visible spectrum, which tissues naturally transmit most effectively and which is non-mutagenic;
- A reliable light source designed to avoid heating and tissue damage.

Systemic porphyrin-based PDT has the major disadvantage of causing prolonged photosensitivity. To avoid severe phototoxicity, the patient is required to avoid sunlight for several weeks after treatment. An alternative approach is the use of topical application of precursors of the endogenous photosensitizer, protoporphyrin IX (PpIX), and other photoactive porphyrins (PAPs). In some countries, PDT with the precursor of PpIX, 5-aminolevulinic acid (5-ALA), has been recognized as an effective and safe treatment of premalignant and malignant skin lesions. However, it has limited ability to penetrate the skin of thicker lesions.[34] Furthermore, although it shows some selectivity in terms of localization in lesions rather than surrounding normal skin, it is far less selective than 5-ALA methyl ester (methyl aminolevulinate; MAL).[33]

As shown in Figure 2, this improved selectivity for tumor tissue by MAL is especially related to the lower build-up of photoactive porphyrins (PAP) in normal skin by topical application of MAL compared with 5-ALA.

Figure 2: Build-Up of Photoactive Porphyrins in Normal Skin Following Application of MAL Cream Versus ALA

Figure 2: Lower build-up of PAP in normal skin after topical application of MAL. The MAL cream and ALA cream were applied topically on 2 adjacent normal skin areas (MAL cream: top and ALA cream: bottom). After 3 hours application, black and white images showed that a lower level of fluorescence (white) of PAP was obtained in MAL-treated area compared with the ALA-treated area.

Greater induction of porphyrins has also been obtained with esters of 5-ALA applied to tumor cells in culture.[35] Lastly, in contrast to topical application of MAL, topical application of ALA on nude mice skin leads to systemic uptake and enhanced systemic levels of photoactive porphyrins (PAP), including in internal organs[31] (Figure 3). Thus, ALA derivatives such as MAL have different abilities to cross biological barriers.

MAL cream is an oil in water emulsion containing methyl aminolevulinate hydrochloride, equivalent to 168 mg/g of methyl aminolevulinate. Outside the USA, the strength of MAL cream is given as 160 mg/g. In the USA, based on a recommendation by FDA, the labeled strength of MAL cream is 168 mg/g. This reflects a 5% overage, and does not represent a difference in strength. Thus the amount of active ingredient by weight is the same in both cases.

Photosensitization following application of MAL cream occurs through the conversion of MAL to PAP, which accumulate in the skin lesions to which MAL cream has been appled. Photoactive porphyrins are concentrated in the mitochondria of proliferating epithelial cells of lesions through the enzymatic pathway of heme synthesis. When the loaded tissue is illuminated with light of the appropriate excitation wavelength, singlet oxygen is produced which results in mitochondrial damage and cell death. Activation of accumulated intracellular porphyrins is achieved by illumination with broadband light in the range 570-670 nm, which is within the visual spectrum.

Figure 3: Systemic Absorption of MAL Versus ALA Cream after Topical Application in Mice

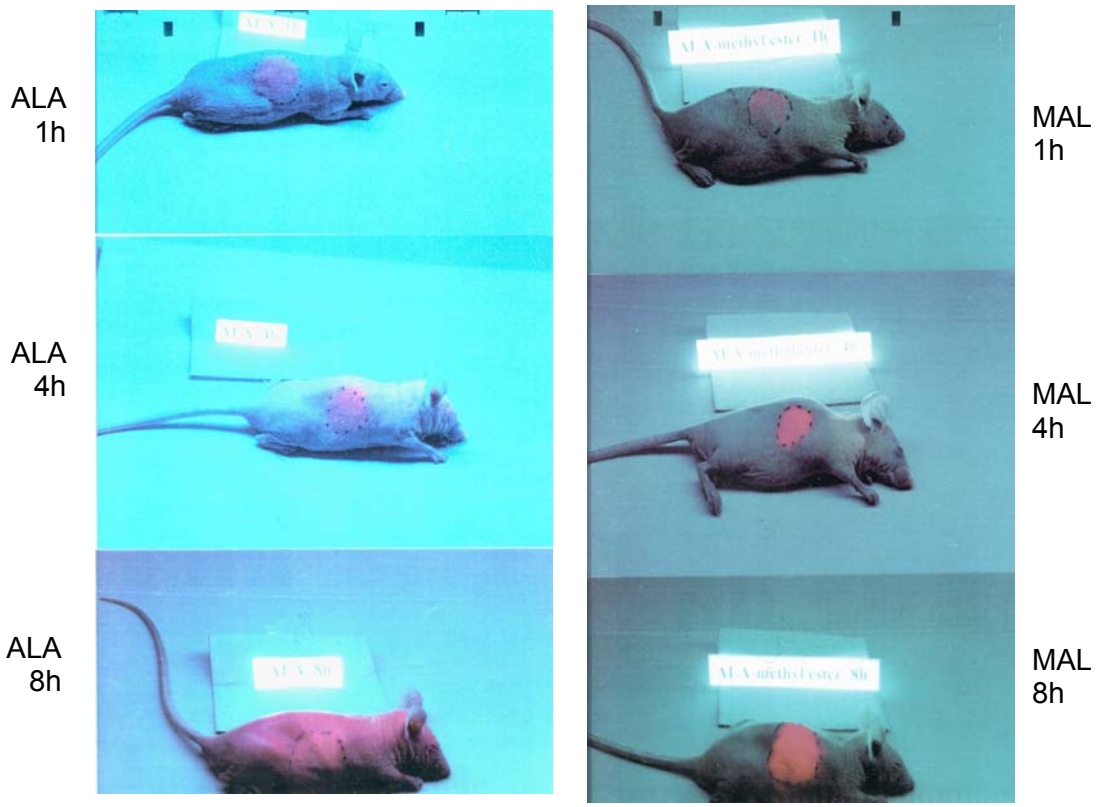


Figure 3: No systemic absorption of MAL after topical application. ALA cream (20%) and MAL cream (20%) was applied to the flank of nude mice and the fluorescence of PAP in the skin was measured at different time points. In ALA treated mice (left panel) the fluorescence (red) was spread to all parts of the mice, while in MAL treated mice (right panel) fluorescence was only observed at the site of application.

Selectivity of the treatment for dysplastic lesions of the skin relative to surrounding skin or other tissues is provided by:

- Application of the cream directly to the lesion;
- Limited penetration of methyl aminolevulinate in normal skin (see Figure 2);
- Preferential accumulation of porphyrins in hyperproliferating cells of lesions (see Figure 4);
- Illumination of the lesion and a thin margin of surrounding tissue only; and
- Rapid clearance of accumulated porphyrins by photoactivation (photobleaching).

Additional potential advantages of MAL-PDT over other recognized treatments are:

- Availability on an outpatient basis for simultaneous treatment of several lesions;
- Improved cosmetic results over current therapies;
- Repeatability; and
- No known systemic toxicity or interaction with other medication.

The use of laser as a light source in PDT may be unsatisfactory, since emission spectra do not include the absorption spectra of intracellular porphyrins, which may contribute to cytotoxicity. The CureLight™ BroadBand light source used in the development program of MAL-PDT (168 mg/g), is easy to manage and less expensive than a laser. The lamp emits red light of the appropriate wavelength band (570 to 670 nm) using a 150-W halogen lamp, and removes infrared light with filters, thus providing an emission spectrum that, unlike laser, includes the absorption spectra of endogenous porphyrins other than PpIX. Red light has better tissue transmission than blue light and therefore achieves photoactivation at a greater depth. The total energy delivered to the lesion is easily controlled and is therefore precise.

Figure 4: Tumor Selectivity of MAL Cream

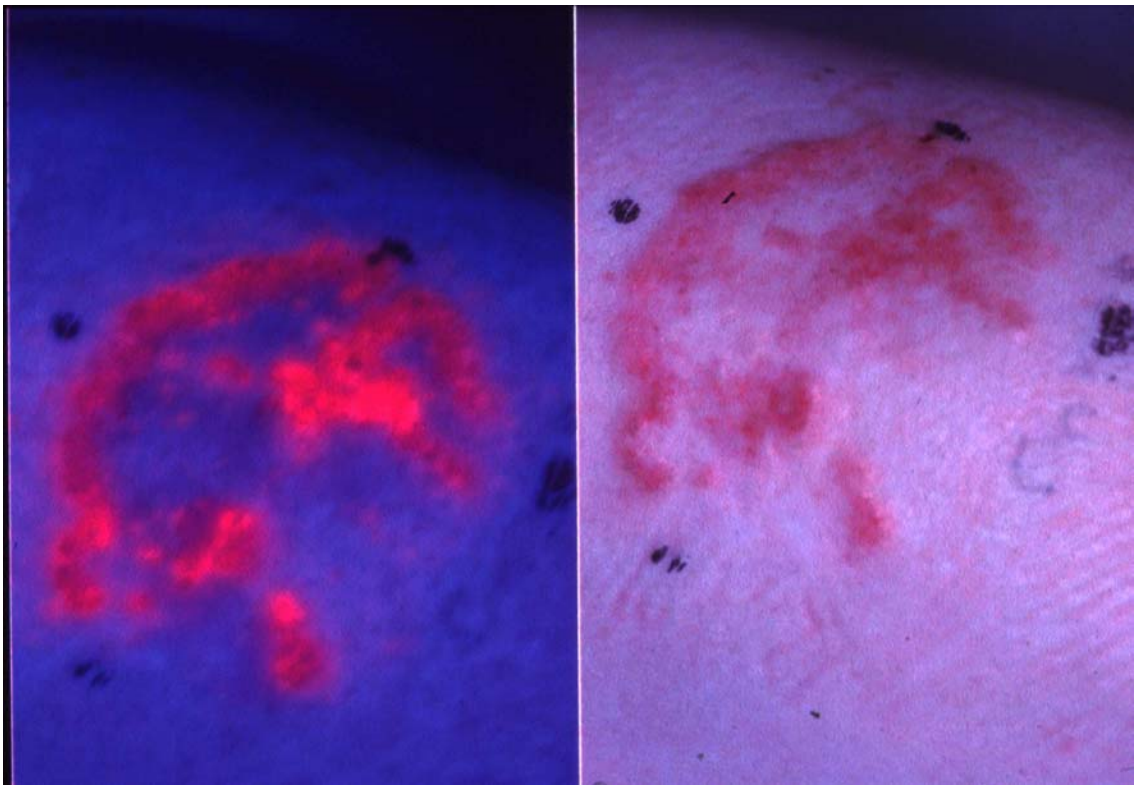
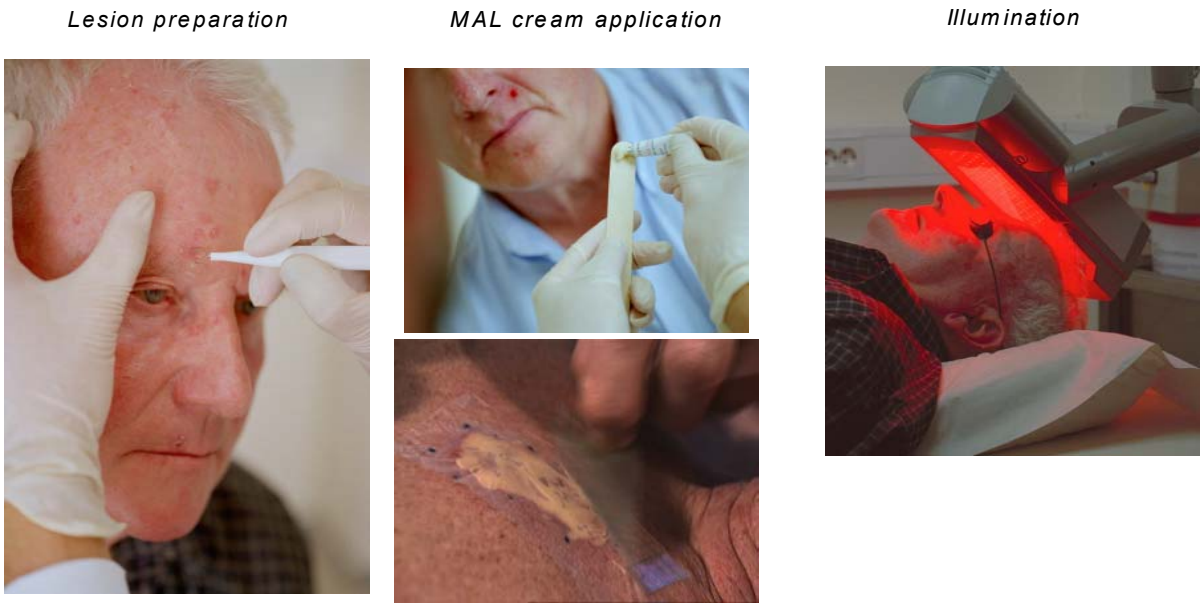


Figure 4: Tumor selectivity of MAL cream. PAP fluorescence (red) in BCC lesion and normal skin after 3 hours MAL cream application (fluorescence picture left and normal white light picture right).

Treatment of BCCs with MAL-PDT involves 3 stages: lesion preparation, application of MAL cream to the lesion and a rim of surrounding normal skin, and illumination (see Figure 5). All stages should be considered an integral part of the MAL-PDT therapy.

Figure 5: MAL-PDT Treatment Stages



3 OVERVIEW OF PRECLINICAL DEVELOPMENT PROGRAM

A complete preclinical program has been conducted to support the use of MAL for the treatment of superficial and nodular basal cell carcinoma.

Pharmacology and toxicology studies have been carried out in different animal models including mice, rats, rabbits, Guinea pigs, and minipigs. *In vitro* models including bacteria, eukaryotic cells, and skin samples have also been used. Skin penetration studies have been performed with human cadaver and rat skin. Most pharmacodynamic and pharmacokinetic studies have investigated the effects of methyl aminolevulinate or MAL cream without photoactivation, while some studies, in particular key toxicology studies, also have assessed the effect of the MAL cream in combination with photoactivating light.

The preclinical development program is summarized in Table 1 through Table 16.

3.1 Pharmacology

Table 1 summarizes the preclinical pharmacology studies. The animal pharmacodynamic studies were conducted to compare the *in vitro* and *in vivo* effects of 5-ALA and its methyl ester with respect to production of intracellular PpIX and sensitization of cells to photoactivation—they assessed the time course of PpIX fluorescence and the relationship between PpIX fluorescence and the dose applied.

In *in vivo* experiments, methyl aminolevulinate administered topically in a cream formulation caused dose-related increases in skin fluorescence, indicating intracellular accumulation of PpIX. The tested dose range was 16 to 160 mg/g. This limitation notwithstanding, the results from the above experiments showed that a plateau of effect was reached with 160 mg/g.

The results of the *in vitro* experiments showed that esterification of 5-ALA enhanced cell penetration and accumulation of PpIX. The protoporphyrin species induced by methyl aminolevulinate is identical to that induced by 5-ALA based on HPLC on cell extracted with perchloric acid/methanol with fluorescence detection. The formed intracellular porphyrin species were localized as well-defined spots in the cytoplasm. Additionally, a diffuse fluorescence was seen in the entire cytoplasm, while practically no fluorescence was found in the nuclear region. Localization of the protoporphyrin was identical regardless of the precursor administered to the cells.

3.2 Acute Toxicity

Table 2 summarizes the results of the acute toxicity studies. The results of these studies established that methyl aminolevulinate has a low order of single-dose oral and intravenous toxicity in mice and rats. The lowest lethal oral acute dose in mice and rats was greater than 2000 mg/kg. The lowest lethal intravenous dose was 840 mg/kg in mice and 1500 mg/kg in rats. The human (systemic) dose after topical application is estimated to be 100 µg (implying about 1.5 µg/kg). Thus, the lowest lethal dose found in rats is

1,000,000 times greater than the estimated human dose. In addition, systemic application of 30 mg/kg of ALA has been shown to be safe.

3.3 Subchronic, Chronic, and Related Toxicity Studies

Table 3, Table 4, and Table 5 summarize the results of the 2 studies of repeated intravenous administration. The results of these repeated dose studies indicate that the liver is the target organ for high intravenous doses of methyl aminolevulinate in male and female rats. A no adverse effect level (NOAEL) in the rat of 200 mg/kg/day when dosed intravenously for 14 consecutive days predicts a wide margin of safety for the topical administration of single or occasionally repeated doses of methyl aminolevulinate.

3.3.1 Hepatotoxicity

The results of repeated-dose studies indicated that the liver was the target organ for high IV doses of methyl aminolevulinate hydrochloride in male and female rats. The no-adverse-effect level (NOAEL) in rats was 200 mg/kg/day when dosed intravenously for 14 consecutive days. Repeated IV doses of 600 mg/kg for 14 days to rats caused decreased hemoglobin, red blood cell count, and packed cell volume, and increased serum levels of protein and cholesterol. Reduced ALP activity, increased ALT activity, and reduced urinary volumes were also noted. Histopathologic examination revealed cholangitis/pericholangitis in animals of both sexes.

It should be noted that although there were indications of moderate hepatotoxicity in rats following the systemic (IV) administration of high doses of methyl aminolevulinate (600 mg/kg/day), no hepatotoxicity was observed following 200 mg/kg/day. This dose represents more than 400 times the maximum clinical dose applied topically.

Furthermore, studies conducted with rats and minipigs designed to study dermal toxicity after treatment with MAL cream, followed by photoactivation, have not indicated any hepatotoxicity. In the microscopic examination of the collected tissues from the minipig study, no treatment-related findings were seen in the evaluated organs. The inflammatory-degenerative changes recorded in the kidneys, liver, lung, adrenals, and testes were considered incidental findings and occurred at the same degree in both the placebo and the MAL cream group.

Routine monitoring of clinical laboratory parameters in humans was performed in 2 dose-finding Phase 2 studies (Studies 202/98 and 203/98), a Phase 3 study (Study 205/98), and 2 small exploratory studies (Studies 101/98 and 204/98). No signs of liver toxicity were observed. The results are provided in Section 8.6.

3.4 Dermal Application

Table 6, Table 7, and Table 8 summarize the 3 studies conducted to assess the tolerance for topically applied MAL cream followed by photoactivation in rats and minipigs. The treatment in these studies mimics the clinical treatment situation, except that the treatments were repeated 4 times. Importantly, the studies assessed both local effects and systemic effects. The first study, using rats, investigated a single treatment, the second

study investigated a four times repeated treatment at the same skin spot in rats, and the third study tested a four times repeated treatment of the same spot in the minipig. A new treatment of the same spot was not commenced until the lesion from the previous treatment was judged as healed when inspected visually.

Application of MAL cream, in the absence of illumination, caused well-defined erythema, which persisted for a few days after treatment. As expected, when combined with illumination, single applications of MAL cream caused slight to severe erythema and up to moderate edema after each treatment. In addition, central wound formation was observed at most application sites and these wounds persisted, as crust formation, until the next treatment.

Repeated dermal applications of MAL cream followed by photoactivation (light illumination) induced epidermal crusts, epidermal hyperplasia, dermal/epidermal inflammation, dermal hemorrhage, and acute wounds (epidermal/dermal coagulation necrosis).

Additional histopathology evaluations were performed on tissues collected in repeated-dose dermal toxicology study conducted in minipigs. The following tissues were evaluated: liver, adrenals, brain, heart, kidneys, lungs, ovaries, pituitary, prostate, spleen, testes, thymus, thyroid, and uterus. The results from histopathology of the sampled internal organs were reported in amendments to the original report.

In the main study animals and the recovery animals, the conclusions from the microscopic examination were that no active treatment-related findings were seen in the evaluated internal organs.

3.5 Special Toxicity Studies

Table 9 summarizes the 2 special toxicity studies that were conducted. In the eye irritation study, all animals exhibited some degree of injection of corneal vasculature but differentiation between MAL-treated and control animals was not possible. Instillation of fluorescein revealed no corneal disruptions in either dosed or control rabbits. Finally, there was no evidence that ambient lighting conditions affected the irritancy or ocular effects of MAL cream.

In the skin sensitization study, methyl aminolevulinate elicited a positive response in 13/20 guinea pigs and inconclusive responses in 5 animals. The results of this experiment indicate that methyl aminolevulinate may cause skin sensitization upon dermal contact.

3.6 Mutagenicity Studies

Table 10 summarizes the mutagenicity studies. The potential for methyl aminolevulinate to induce mutagenicity and/or genotoxicity was assessed through the use of 3 *in vitro* and 1 *in vivo* models. In addition to the usual protocols for these experiments the *in vitro* tests were modified to allow for incorporation of light exposure of methyl aminolevulinate exposed cells.

Methyl aminolevulinate alone or in combination with a microsomal activating system produced no evidence of mutagenic potential in commonly used bacterial strains (TA 98, TA 100, TA 1535, TA 1537, WP2 pKM101, WP2uvrA pKM101). When methyl aminolevulinate exposed test systems were exposed to light, unequivocal cytotoxicity was evident, but even at cytotoxic doses there was no evidence of mutagenicity. Similarly, Chinese hamster ovary cells exposed to methyl aminolevulinate in the presence of light (5 or 50 J/cm^2) exhibited marked cytotoxicity but no clastogenicity. Intravenously administered methyl aminolevulinate did not induce micronuclei in the bone marrow of rats.

3.7 Reproductive Studies

No study of the potential toxicity of methyl aminolevulinate to the reproductive function or of the potential embryo-fetal or perinatal toxicity has been conducted. This is considered justified since it has been demonstrated that the systemic exposure after topical application of methyl aminolevulinate is negligible.

3.8 Carcinogenicity Studies

No formal Good Laboratory Practice (GLP) study has been conducted to assess the potential of methyl aminolevulinate to cause cancer. This is considered justified because the treatment is only given once or twice, the mutagenicity studies showed negative results, and systemic exposure is negligible.

3.9 Absorption, Distribution, Metabolism, Excretion

Table 11 through Table 16 summarize the preclinical absorption, distribution, metabolism, and excretion (ADME) studies. The metabolites 5-ALA or PpIX were not detected in tissue other than the skin application site after single dose topical application of methyl aminolevulinate to rats (non-abraded skin). Only after repeated dosing with subsequent photoactivation of rats, could slightly elevated levels of 5-ALA be measured in serum. No signs of systemic toxicity were seen.

Use of ^{14}C-methyl aminolevulinate in topical application to rats for 48 hours resulted in 13.1% and 6.4% systemic absorption through abraded and non-abraded skin respectively. The major fraction of this was collected in excreta and the remaining fraction was concentrated to kidney/bladder and intestine content, indicating that it was on its way to be excreted. It was also found that the fraction remaining at the skin application site was 6.3% (abraded) and 8.4% (non-abraded) after 24 hours exposure.

The *in vitro* study showed that human skin had a much lower permeability for ^{14}C-methyl aminolevulinate than the rat skin. The systemic absorption through human skin of only 0.26% of the applied dose after 24 hours application, means that only 1.74 mg of a human dose of 672 mg MAL (4 g cream) will be absorbed systemically after this period.

In the clinical situation a 3-hour application period is used. Assuming a 1.6-hour lag phase, this means that only 1.74 mg x (3-1.6)/24 = 0.101 mg ≈ 100 μg (or 1.5 μg/kg) of a

human dose of 672 mg MAL (4 g cream) will be absorbed systemically. This amount is considered to be negligible.

It was found in the *in vitro* penetration study that the fraction of radioactivity forming a depot in the skin was 9.449% for the rat skin after 24 hours exposure. This corresponds well with the findings from the *in vivo* excretion experiment in which 8.4% of the applied dose was found in the skin.

It is concluded that adequate amounts of methyl aminolevulinate are absorbed into the epidermis of the skin, the site of action of the drug. Adequate local epidermal exposure has been shown, while systemic exposure to methyl aminolevulinate after topical application is negligible.

3.10 Discussion

The results of preclinical toxicology data predicted that methyl aminolevulinate cream 168 mg/g would be safe for topical use by humans. The results of clinical studies are consistent with the preclinical data. As summarized in Section 8, none of the clinical studies have shown any evidence of systemic toxicity. There were few non-local adverse events, and, although a relationship to treatment could not be ruled out in all cases, it should be noted that a similar frequency of non-local adverse events was observed in the placebo, surgery, and cryotherapy groups. The majority of adverse effects was attributable to expected phototoxicity and occurred during or after illumination. Although most lesions treated in the clinical studies were on the face or scalp, no evidence of ocular toxicity was observed. The potential for methyl aminolevulinate cream 168 mg/g to elicit irritancy and allergenicity was examined further in clinical Studies 107/01, 108/01, and 110/03.

3.11 Conclusions

- Methyl aminolevulinate acts as a precursor of heme biosynthesis and causes intracellular accumulation of photoactive porphyrins in both in vivo and in vitro models. Accumulated intracellular porphyrins can be used in PDT.
- Single or repeated, oral, intravenous or topical doses of methyl aminolevulinate were well tolerated by mice, rats, and minipigs indicating a low potential for systemic toxicity. The NOAEL after repeated intravenous administration for 14 consecutive days was 200 mg/kg/day.
- Single or repeated topical applications of methyl aminolevulinate followed by photoactivation cause clear but reversible dermal lesions in rats and minipigs but with no evidence of systemic toxicity in either species.
- The pharmacokinetic investigations in animal models have documented that the systemic absorption of methyl aminolevulinate and its metabolites is minimal, and an *in vitro* model has shown that the human skin is even less permeable to these compounds. The systemic absorption and exposure of humans after dermal treatment is negligible.

- From the specification of the active pharmaceutical ingredient methyl aminolevulinate and the drug product MAL cream, there are no impurities or degradation products that should exclude the product from the intended use.
- There is no indication that methyl aminolevulinate or its metabolites are genotoxic, neither with nor without photoactivation.
- MAL cream is not irritating to the eye, but has been shown in guinea pigs, the potential to cause delayed contact hypersensitivity.

Thus, the results of the preclinical studies show that MAL cream has a high potential for safe therapeutic application in PDT of premalignant and malignant neoplasms of human skin.

Table 1: Pharmacology Studies

Study Title (Study Report)	Test model	Route of admin.	Dosing	Primary Pharmacological Action	Secondary Pharmacological Action
Formation of PpIX in murine skin after topical application of cream formulations containing different concentrations of P-1202 (*Report FT-18*)	Female Balb/c athymic nude mice	Applied to skin	Creams contained 16, 80 or 160 mg/g of methyl aminolevulinate. A spot of cream was applied to each flank on each mouse.	Methyl aminolevulinate caused dose-related increase in PpIX in skin	None observed
Formation of PpIX in murine skin after topical application of P-1202 in different cream formulations (*Report FT-13*)	Female Balb/c athymic nude mice	Applied to skin	Five cream formulations each containing 16 or 160 mg/g of methyl aminolevulinate. About 0.5 g of cream was applied to about 2 cm^2 on flank	Dose-related increase in fluorescence with maximum effect at about 10 hr	None observed
Comparison of PpIX formation after ALA and ALA methyl ester addition to cell cultures. (*Report FT-40*)	Human tumor cells (WiDr and NHIK 3025) and Chinese hamster fibroblasts	Added to medium	1 and 2 mM 5-ALA or methyl aminolevulinate for 4 hr. Irradiation with fluorescent light (15 W/m^2)	Methyl aminolevulinate caused more PpIX formation than 5-ALA. No significant amounts of other porphyrins were detected. Cells were sensitized to light.	None observed

Table 2: Acute Toxicity Studies

Study Title (Study Report)	Species	Sex / age	Dose range (mg/kg bw)	Route of Adm. / Vehicle	Toxic signs	Lethal doses (mg/kg bw)	Time to death
Single dose oral toxicity study in the mouse. (*Report 1458/8-1032*	Mouse	Males / 5-7 weeks Females / 5-7 weeks	2000	Oral (gavage) / purified water	Pilo-erection in 2 males and 3 females	None	Not applicable
Single dose intravenous toxicity study in the mouse. (*Report 1555/003-1032*)	Mouse	Males / 6-7 weeks Females / 6-7 weeks	585 - 2000	Intravenous / physiological saline	Lethargy, pilo-erection, gasping proneness, tachypnea	840 1000 2000	15 min Immediately Immediately
Single dose oral toxicity study in the rat. (*Report 1458/7-1032*)	Rat	Males / 6-8 weeks Females / 6-8 weeks	2000	Oral (gavage) / purified water	None	None	Not applicable
Single dose intravenous toxicity study in the rat. (*Report 1555/002-1032*)	Rat	11 males / 7-9 weeks 11 females / 10-11 weeks	1000 – 2000	Intravenous / physiological saline	Lethargy, salivation. Isolated cases of breathing pattern changes, tachypnea, bradypnea, dyspnea, pilo-erection, anogenital soiling	1500 2000	During dosing (<1/2 hour) Immediately

Table 3: Design of Studies for Repeated Intravenous Administration (Studies 1555/7 and 1555/8)

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Doses	Dose schedule	Route of administration	Vehicle
7-day intravenous dose-range finding toxicity study in the rat (*Report 1555/7-D6144*)	Rat / Crl:CD.BR	9 males (6 weeks) 9 females (6 weeks)	0, 250, 750 mg/kg/day	Dosed daily for 7 consecutive days	Intravenous	Sterile physiological saline
14-day intravenous toxicity study in the rat. (*Report 1555/8-D6144*)	Rat / Crl:CD.BR	10/sex/dose 80 animals used	0, 50, 200, 800 (600) mg/kg/day	Dosed daily for 14 days then observed for one day after final dose.	Intravenous	Sterile physiological saline

Table 4: Dose-Related Changes After 7-Day Repeated Intravenous Administration (Study 1555/7)

Study Title (Study Report)	Doses (mg/kg/ day)	Survival	Weight gain	Toxic signs	Hematology (day 6)	Clinical chemistry	Change in organ wt	Pathological findings (macroscopic findings)
7-day intravenous dose-range finding toxicity study in the rat (*Report 1555/7-D6144*)	0	6/6		None				Apparent changes showed no trend consistent with a treatment-related effect on any target organ. Such changes included dark foci on the lungs of one male dosed with 750 mg/kg/day and a clear cyst on the kidneys of a second male in this group.
	250	6/6	NSC	Red brown staining of nose and mouth	NSC		T/E: - 10%	
	750	6/6	NSC	Red brown staining of nose and mouth	NSC	Bilirubin levels were significantly elevated (males and females). Decreased levels of urea and BUN (females)	T/E: -13%	

NSC: No significant change; BUN: Blood urea nitrogen; T/E: testes/epididymides (males);
*: no notable change

Table 5: Dose-Related changes after 14-Day Repeated Intravenous Administration (Study 1555/8)

Study Title (Study Report)	Doses (mg/kg/day)	Survival M F	Weight gain	Toxic signs	Hematology (day 13)	Clinical chemistry
14-day intravenous toxicity study in the rat. (*Report 1555/8-D6144*)	0	10/10 10/10		None		
	50	10/10 10/10	NSC	None	NSC	NSC
	200	10/10 10/10	NSC	None	NSC	NSC
	600	10/10 10/10	NSC	Red brown staining of the mouth, salivation noisy respiration, pilo-erection, ataxia	Decreased red blood cell counts, hemoglobin and packed cell volumes	Increased levels of bilirubin, total protein, cholesterol, alkaline phosphatase and alanine transferase
	(800)[§]	9/10 10/10	NSC	Labored or noisy respiration, ataxia, bulging eyes, salivation		

§ Changed to 600 mg/kg/day after death of one male on day 2; NSC: No significant change;

Dose-Related changes after 14-Day Repeated Intravenous Administration (Study 1555/8) (Continued)

Study Title (Study Report)	Doses (mg/kg/day)	Change in organ wt	Pathological findings (macroscopic findings)
14-day intravenous toxicity study in the rat (*Report 1555/8-D6144*)	0		
	50	AMLW (m) ↑ AMSW (f) ↓	None
	200	AMLW (m) ↑, AMLW (f) ↑,	None
	600	AMLW (m) ↑, AMLW (f) ↑,	Minor cholangitis/pericholangitis. Possibly due to the finding of enlarged livers (esp. males).
	(800)§		

§ Changed to 600 mg/kg/day after death of one male on day 2; AMLW: Adjusted mean liver weight; AMSW: Adjusted mean spleen weight; m: males; f: females

Table 6: Study of Single Dermal Application with Photoactivation

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Doses Conc.	Duration	Photoact.	Route of admin/	Vehicle	Pathological findings (macroscopic findings)
Single dose dermal toxicity in the rat with integral photoactivation procedures (*Report 1555/001-1032*)	Rat / Crl:CD.BR	55 males (7-9 weeks) 55 females (10-11 weeks)	0 160 mg/g 160 mg/g 16 mg/g 160 mg/g	12 hr 12 hr 12 hr 12 hr 36 hr	200 J/cm^2 100 J/cm^2 200 J/cm^2 100 J/cm^2 100 J/cm^2	Dermal	Unguentum Merck	Interim sacrifices were performed on days 3, 8 and 15. No systemic toxicity was found. Dose-related erythema, edema, hyper-keratinization, scab, escar, necrosis and fissuring were observed. Histopathology confirmed inflammation. Healing observed during 15 days.

Table 7: Study of Repeated Dermal Application with Photoactivation

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Doses Conc.	Duration	Photoact.	Route of admin.	Schedule	Vehicle	Pathological findings (macroscopic findings)
Repeated application dermal toxicity study in the rat with integral photoactivation procedure (*Report 1555/005-1032*)	Male and female rats, Crl:CD.BR	50 males (10-11 weeks) 50 females (13-15 weeks)	0 160 mg/g 16 mg/g 80 mg/g 160 mg/g	24 hours 24 hours 24 hours 24 hours 24 hours	100 J/cm^2 0 J/cm^2 100 J/cm^2 100 J/cm^2 100 J/cm^2	Dermal	Treatment administered on days 1, 11, 29 and 43 (males) 48 (females)	MAL base cream	No systemic toxicity. Site of application showed treatment dependent erythema, edema, hyperkera-tinization, escar, hemorrhage and bruising

Table 8: Study of Repeated Dermal Application with Photoactivation

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Doses Conc.	Duration	Photoact.	Route of admin.	Schedule	Vehicle	Pathological findings (macroscopic findings)
Repeated dose dermal toxicity study with integral photoactivation in minipigs (*Report 35635*)	Göttingen SPF minipigs	8 males and 8 females (3-4 months)	0 0 160 mg/g 160 mg/g	3 hours 3 hours 3 hours 3 hours	0 J/cm^2 75 J/cm^2 0 J/cm^2 75 J/cm^2	Dermal Dermal Dermal Dermal	Four doses, 12 to 26 days apart. Animals were observed for 3 or 15 days after final dose, then sacrificed	MAL base cream	No evidence of systemic toxicity. MAL cream (no illumination), caused well-defined erythema which persisted for a few days after treatment. When combined with illumination, single applications of MAL cream caused slight to severe erythema and up to moderate edema after each treatment. Repeated dermal applications of MAL cream followed by illumination induced epidermal crusts, epidermal hyperplasia, dermal/epidermal inflammation, dermal hemorrhage, and acute wounds (epidermal/dermal coagulation necrosis). Repeated applications of MAL cream without photoactivation caused a slight chronic dermatitis which was reversible during the recovery period. Thus, both the formulation and light activation cause a local reaction but the reaction is more severe after light activation. Reversible skin lesions were produced.

Table 9: Special Studies Conducted to Assess Local Irritancy and Immunostimulation Induced by Methyl Aminolevulinate

Study Title (Study Report)	Species/ Strain	No./sex/grp (Total No.)	Route of Administration	Treatment Regimen	Duration of dosing/observation	Results
Eye irritation in the rabbit (*Report 1555/009-D6144*)	New Zealand White Rabbits,	2 females, 7 males 3 animals per group. Totally 9 rabbits	Instillation of cream into conjunctival sac	0.1 ml of placebo or methyl aminolevulinate (168 mg/g) containing cream	Single instillation. Animals maintained in reduced light and ambient light and observed for 72 hours.	No evidence of irritation by methyl aminolevulinate
Skin sensitization study in the Guinea pig. (*Report 1555/004-1032*)	Female Guinea Pig/ Dunkin-Hartley	10 females in control group, 20 females in test group	Intradermal injection and dermal application	Animals received intradermal injection on day 1, dermal applications on day 8 and final dermal challenge on day 22.	Dermal response was graded 24 and 48 hours after challenge	Methyl aminolevulinate elicited a positive reaction in 13/20 animals with inconclusive reactions in 5.

Table 10: Mutagenicity Studies

Study Title (Study Report)	Test system	Metabolizing System	Concentrations tested	Contact/ Incubation time	Positive Control	Results
Reverse mutation in four histidine-requiring strains of *S. typhimurium* and two tryptophan-requiring strains of *E coli*. (*Report 1458/11-1052*)	Tester strains TA98, TA100, TA1535, TA1537, WP2 pKM101 and WP2uvrA pKM101.	+/- S9-mix	Maximum dose: 5000 μg/plate	3 days	TA98:2-nitrofluorene TA100: Na Azide TA1535: Na Azide TA1537: 9 aminocridine WP2pKM101:4-nitroquinoline 1-oxide WP2 uvrA:2-aminoanthracene.	No evidence of mutagenicity
Reverse mutation in three histidine-requiring strains of *S. typhimurium* and one tryptophan-requiring strains of *E coli* in the presence of visible light. (*Report 1458/12-1052*)	Tester strains TA98, TA100, TA1537, WP2pKM101	None	Maximum dose: 5000 μg/ml. Maximum light dose: 100 J/cm^2	Preincubation 3 hr, irradiation with up to 100 J/cm^2 and incubation for 3 days after removal of test compound	TA98:2-nitrofluorene TA100: 4-nitroquinoline 1-oxide TA1537: ICR-191 WP2pKM101:N-methyl-N'-nitro-N-nitrosoguanidine and 8-methoxypsoralen.	Clear evidence of phototoxicity but no photomutagenic activity
Induction of chromosome aberrations in cultured Chinese hamster ovary cells in the presence of visible light. (*Report 1458/13-D5140*)	Chinese hamster ovary (CHO) cells	None	Maximum concentration: 1816 μg/ml. Light dose: 5 or 50 J/cm^2	Preincubation 4 hr, irradiation with up to 50 J/cm^2 and 16 hr recovery after removal of test compound.	4-nintroquinoline 1-oxide and 8-methoxypsoralen.	Marked cytotoxicity at highest light dose. No chromosomal aberrations or clastogenic effects observed.
Induction of micronuclei in bone marrow of treated rats. (*Report 1458/24-D5140*)	Male Rats/Crl:Han Wist (Glx:BRL)BR	N/A	250, 500 and 1000 mg/kg administered intravenously on two consecutive days.	Samples taken 24-hours after second dose	Cyclophosphamide, 40 mg/kg, intravenously 24-hours prior to sample collection	Unequivocal signs of cytotoxicity in high dose methyl aminolevulinate rats. No evidence of micronuclei induction.

Table 11: Skin Fluorescence After Systemic Administration

Study Title Study Report	Species/ Strain	Animals/ group (Total)	Route of administration	Dose	Compound Measured (Method)	Results
ALA and ALA-esters: Skin build-up after IV or IP injection. (*Report A-1.2A*)	Female Mice, Balb/c athymic nude	5 per dose, 30 animals used	Intravenous or intraperitoneal	50, 150, or 250 mg/kg	PpIX formation in skin monitored by its fluorescence at 632 nm	5-ALA produced greater fluorescence than the esters. Fluorescence appeared earlier and with a sharper peak after 5-ALA administration than after administration of methyl aminolevulinate.
PpIX formation n mouse skin after administration of P-1202. Oral vs. intraperitoneal administration. (*ReportFT-11*)	Mice, Balb/c nu/nu nude	5 per group, 20 animals used	Oral or intraperitoneal	1.5 mmole/kg (250 mg/kg ALA and 272 mg/kg methyl amino-levulinate)	PpIX formation in skin monitored by its fluorescence at 632 nm	ALA produced significantly more and long-lasting fluorescence than did the ester.

Table 12: Blood Levels of 5-ALA and PpIX After Single Dermal Application

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Doses Conc.	Duration	Photoact.	5-ALA levels*	Results (PpIX levels*)
Single dose dermal toxicity in the rat with integral photoactivation procedures (*Report 1555/001-1032*)	Rat / Crl:CD.BR	55 males (7-9 weeks) 55 females (10-11 weeks)	0 160 mg/g 160 mg/g 16 mg/g 160 mg/g	12 hr 12 hr 12 hr 12 hr 36 hr	200 J/cm^2 100 J/cm^2 200 J/cm^2 100 J/cm^2 100 J/cm^2	Negligible for all groups	Negligible for all groups

* Blood sample taken immediately after removal of cream, i.e. before photoactivation

Table 13: Blood Levels of 5-ALA and PpIX After Repeated Dermal Application with Integral Photoactivation

Study Title (Study Report)	Species/ Strain	No. / sex (age)	Dosing Conc	Duration	Photoact.	5-ALA (1)* ng/ml	5-ALA (4)* ng/ml	PpIX (1)* ng/ml	PpIX (4)* ng
Repeated application dermal toxicity study in the rat with integral photoactivation procedure (*Report 1555/005-1032*)	Male and female rats, Crl:CD.BR	50 males (10-11 weeks) 50 females (13-15 weeks)	0	24 hours	100 J/cm^2	14 ± 2	ND**	ND	ND
			160 mg/g	24 hours	100 J/cm^2	28 ± 12	250 ± 125	15 ± 18	10 ± 4
			16 mg/g	24 hours	100 J/cm^2	ND	ND	ND	ND
			80 mg/g	24 hours	100 J/cm^2	ND	ND	ND	ND
			160 mg/g	24 hours	100 J/cm^2	23 ± 7	179 ± 162	20 ± 28	27 ± 32

(1): Immediately after cream removal - first treatment; (4): Immediately after cream removal - fourth treatment; * data shown as median ± SD; ** Not determined

Table 14: Skin Localization After Dermal Application

Study type (Study Report)	Species/ Strain	Animals/ group (Total)	Route of administration	Dose	Compound Measured (Method)	Results
Biolocalization of 5-ALA and ALA methyl ester induced porphyrins in normal mouse skin (*Report FT-39*)	F Balb/c nu/nu athymic nude mice	5 mice /group; total 20	Topical application of cream containing: a) 148 mg/g ALA or b) 160 mg/g methyl aminolevulinate	0.1 g cream applied onto a 2.25 cm2 area	Fluorescence microscopy of frozen sections taken from treated mouse skin samples	No fluorescence in control. Porphyrin fluorescence noted in epidermis, epithelial hair follicles and sebaceous glands but not dermis. Fluorescence intensity increased with time with max seen at 6 hours post treatment.

Table 15: Absorption, Distribution and Excretion after Dermal Application

Study type (Study Report)	Species/ Strain	Animals/ group (Total)	Route of administration	Dose	Compound Measured (Method)	Results
Quantitative whole-body autoradiography and excretion of radioactivity following topical administration of ^{14}C-P-1202 cream to the rat (*Report1555/10-D11407*)	Male albino rats	3 /group; total 12	Topical administration of ^{14}C-P-1202 to rats with abraded or non-abraded skin.	300 mg cream / animal (48 mg of methyl amino-levulinate per animal)	Whole body autoradiography. (Animals sacrificed at 3,8, 24 hours post-dose) Absorption / Excretion. Animals sacrificed at 48 hours post-dose	Tissue radioactivity was well distributed. Conc. low at all sampling times. Abraded: 10% of admin radioactivity recovered in excreta (6.5% in urine) and 3% in carcass for total of 13% recovery. Non-Abraded: 4.5% of admin radioactivity recovered in excreta (3% in urine) and 2% in carcass for total of 6.4% recovery.

Table 16: In Vitro Skin Penetration

Study type (Study Report)	Species/ Strain	Animals/ group (Total)	Route of admin.	Dose	Compound Measured (Method)	Results
^{14}C-P-1202 Cream: Rates of penetration through human and rat skin using a static *in vitro* system. (*Report 1555/13*)	Human cadaver back skin and Sprague-Dawley dorso-lumbar skin samples	N/A	Topical (Penetration of ^{14}C through excised skin)	Cream containing 48 mg/g ^{14}C-methyl aminolevulinate applied to the skin for 24 hours	Quantitated ^{14}C in receptor fluid and skin.	Approximately 10-fold more ^{14}C penetrated rat skin than human skin. After 24 hours, 2.097% and 0.26% of the applied dose penetrated rat and human skin, respectively. Furthermore, 9.449% and 4.9% of the dose formed a depot in rat and human skin, respectively.

4 OVERVIEW OF CLINICAL DEVELOPMENT PROGRAM

The New Drug Application (NDA) for photodynamic therapy (PDT) with MAL cream for use in basal cell carcinoma (BCC) was filed with the Food and Drug Administration (FDA) on 21 February 2003 (NDA 21-756).

The development program for MAL-PDT (Figure 6 and Figure 7) has been designed to include a wide spectrum of BCC disease, including low-risk and high-risk superficial and nodular BCC and includes placebo- and active-controlled studies.

The program has focused on developing an alternative treatment for BCC that meets the clinical goals of tumor removal, tissue preservation, and cosmesis. Prior to the initiation of the clinical trials, a multifactorial program was conducted to determine the relationship between dose (concentration of the applied cream), duration of exposure to the cream, and the duration of exposure to the light activation. These data were required for the design of the clinical trials for the use of MAL-PDT in the treatment of both actinic keratosis (AK), subject to a separate application, and BCC. With this information, it was then possible to design clinical trials to evaluate the safety and efficacy of MAL-PDT.

The Phase III program was comprised of 6 studies as follows:

- Two double-blind, randomized, placebo-controlled trials in patients with low-risk nodular lesions (Studies 307/00 and 308/00);
- One open, randomized, controlled trial with simple surgical excision as comparator in patients with low-risk nodular lesions (Study 303/99);
- One open, randomized, controlled trial with cryotherapy as comparator in patients with low-risk superficial lesions (Study 304/99); and
- Two uncontrolled studies in high-risk patients unsuitable for conventional therapy (Studies 205/98 and 310/00).

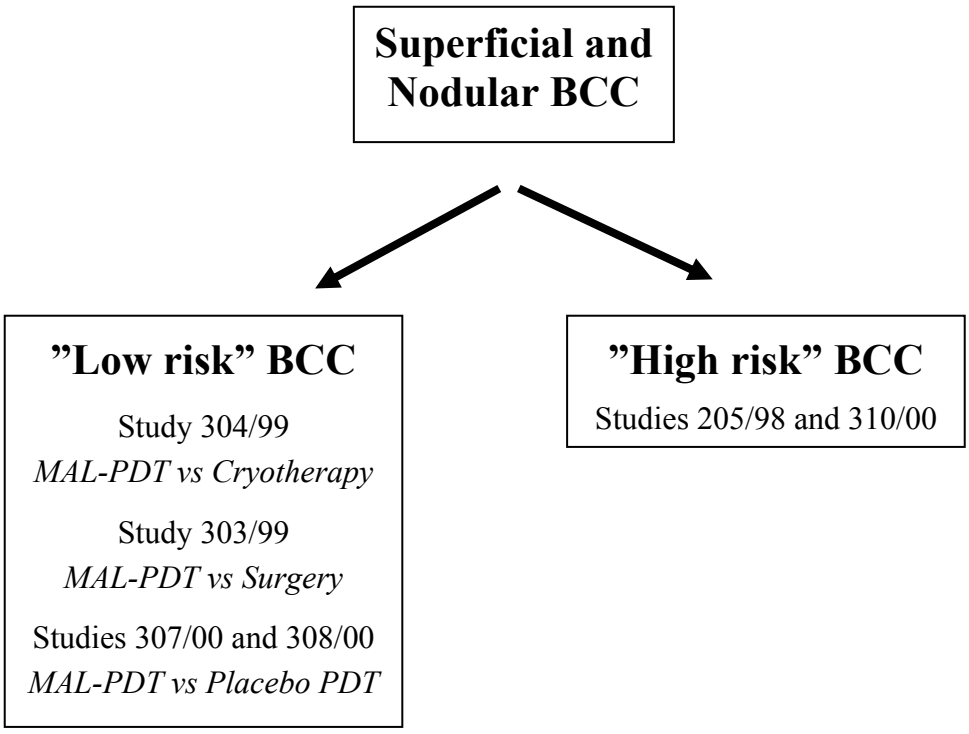
As outlined in Figure 6, this program was designed to demonstrate efficacy and safety for treatment with MAL-PDT in 2 distinct BCC populations, namely superficial and nodular low-risk and high-risk BCC.

These studies confirm that MAL-PDT is safe and effective in meeting the treatment goals of tumor removal, tissue preservation, and cosmesis in low-risk and high-risk superficial and nodular BCC.

The integrated summary of safety (ISS) for the BCC application focused primarily on the results of placebo-controlled and active-controlled Phase III studies in patients with primary nodular and superficial BCC and secondarily on the results of studies in BCC patients unsuitable for conventional therapy due to potential morbidity or poor cosmetic outcome (high-risk patients). Additional safety data for patients with actinic keratosis (AK), a compassionate use program (Study 001/97), and data for other studies were also included to present a complete assessment of the safety profile of PDT with MAL cream (MAL-PDT).

A separate NDA for PDT with MAL cream for use in AK was filed with FDA on 29 September 2001 (NDA 21-415) with a 120-day Safety Update provided on 17 January 2002. A 120-day Safety Update for the BCC indication was submitted on July 16, 2003.

Figure 6: Phase III Clinical Development Program for BCC



References: Randle et al.,[16] Swanson et al.,[30] and Martinez et al.[20]

Figure 7 provides a more detailed overview of the overall clinical development program for MAL-PDT in BCC. The designs of these studies are summarized in Table 17.

Studies 202/98, 301/99, 302/99, 305/99, and 306/99 were conducted for the AK indication but were included in the BCC ISS submission to support safety. The other studies (101/97, 206/98, 203/98, 205/98, 310/00, 303/99, 304/99, 307/00, and 308/00) were included in the ISE submission for BCC to support efficacy and safety.

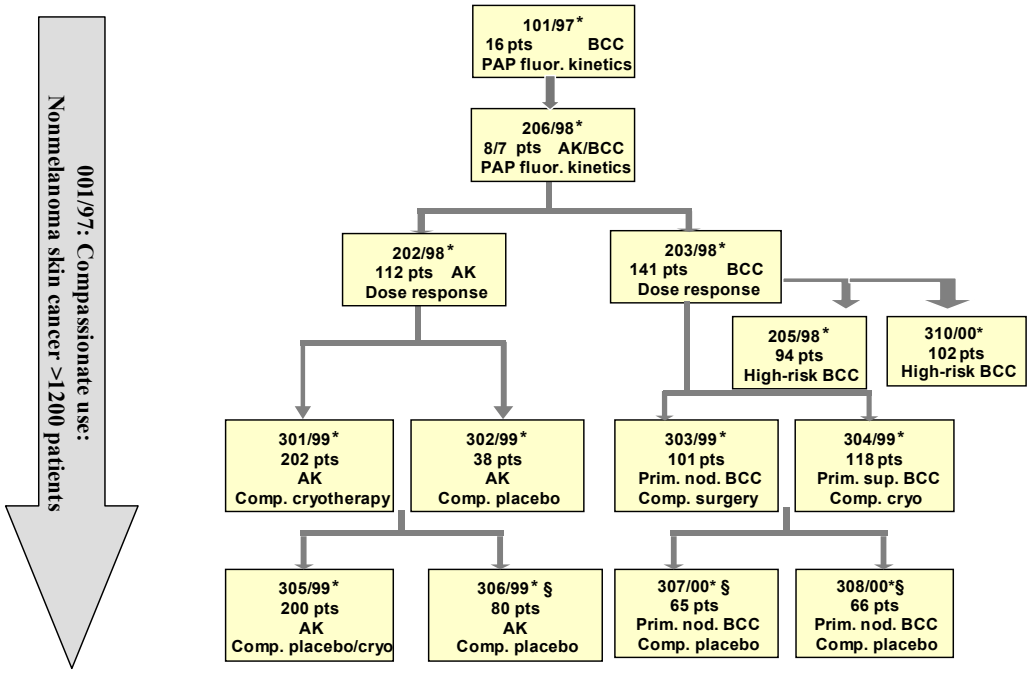


Figure 7: Clinical Development of MAL-PDT in BCC

Number of patients = number of treated patients. Pts = patients; PAP = photoactive porphyrins; comp = comparator; fluor = fluorescence; cryo = cryotherapy; prim =primary; sup = superficial.

* In ISS database and Update pooled database; § Submitted under an IND (#59,756 for Study 306/99 [AK] and #59,221 for Studies 307/00 and 308/00 [BCC]).

Table 17: Table of Studies in the ISS

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)
Studies in Basal Cell Carcinoma							
Placebo-Controlled, Phase III							
PC T307/00 Dec 2000 to April 2002 Report July 2002	US Tope	Primary nodular BCC	Phase III, double-blind, randomized, parallel-group, multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	2 treatments, 7 days apart; if partial response at 3-month follow-up, another treatment cycle was given; 6 months after last PDT all treated areas were excised for histological examination of response	65 65 (28-88) Methyl aminolevulinate cream: 62 (28-88) Placebo: 67 (39-88) Type I: 19 (29%) Type II: 32 (49%) Type ≥III: 14 (22%)	50 M, 15 F 65 C Methyl aminolevulinate cream: 25 M, 8 F Placebo 25 M, 7 F
PC T308/00 October 2000 to September 2002 Report November 2002	Australia Foley	Primary nodular BCC	Phase III, double-blind, randomized, parallel-group, multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	2 treatments, 7 days apart; if partial response at 3-month follow-up, another treatment cycle was given; 6 months after last PDT all treated areas were excised for histological examination of response	66 68 (40-88) Methyl aminolevulinate cream: 70 (48-87) Placebo: 66 (40-88) Type I: 27 (41%) Type II: 22 (33%) Type ≥III: 17 (26%)	49 M, 17 F 66 C Methyl aminolevulinate cream: 22 M, 11 F Placebo: 27 M, 6 F
Active-Controlled, Phase III							
PC T303/99 ongoing Reports Initial – April 2002 3 m – April 2002 12 m – April 2002 24 m – November 2002	UK, France, Sweden, Norway, Netherlands, Austria Rhodes (UK)	Primary nodular BCC	Phase III, open, randomized, parallel-group, multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm) Surgical excision was performed according to the investigator's routine with 5-mm margins	2 treatments, 7 days apart; if treatment failure at 3-month follow-up, another treatment cycle was given or the lesion was surgically excised	101 38-95 (68) Methyl aminolevulinate cream: 40-95 (69) Surg: 38-82 (67) Type I: 8 (8%) Type II: 47 (47%) Type ≥III: 46 (46%)	61 M, 40 F, 100 C, 1 other, Methyl aminolevulinate cream: 32 M, 20 F Surg: 29 M, 20 F

Table 17: Table of Studies in the ISS

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)
PC T304/99 ongoing Reports Initial – May 2001 12 m – November 2002 24 m – November 2002	France, Italy, Sweden, UK, Belgium, Finland, Austria Basset-Seguin (France)	Primary superficial BCC	Phase III, open, randomized, parallel-group, multicenter	Methyl aminolevulinate cream: 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm) Cryotherapy: standard liquid nitrogen spray; Two freeze thaw cycles	1 treatment; if treatment failure at 3-month follow-up, a treatment cycle was given Methyl aminolevulinate cream: Second cycle was 2 treatments 1 week apart Cryotherapy: Second cycle same as first	118 25-90 (64) Methyl aminolevulinate cream: 25-87 (63) Cryo: 38-90 (64) Type I: 6 (5%) Type II: 71 (60%) Type ≥III: 41 (34%)	70 M, 48 F 118 C Methyl aminolevulinate cream: 40 M, 20 F Cryo: 30 M, 28 F
Unsuitable for Conventional Therapy							
PC T205/98 ongoing Reports Initial – December 2000 12 m – December 2000 24 m – June 2002	Sweden, Norway, UK, Denmark, Austria, Germany, Netherlands Larkö (Sweden)	Superficial and nodular BCC lesion unsuitable for traditional therapy due to possible morbidity or poor cosmetic outcome	Phase II, open, non--comparative, multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	2 treatments, 7 days apart; if treatment failure at 3-month follow-up, or partial response at 6-month follow-up, another treatment cycle was given Methyl aminolevulinate cream applied 3 h before illumination	94 32-93 (68) Fitzpatrick skin type not assessed	57 M, 37 F 94 C
PC T310/00 ongoing Reports Initial – January 2002 12 m – September 2002	Australia Vinciullo	Superficial and nodular BCC lesion unsuitable for traditional therapy due to possible morbidity or poor cosmetic outcome	Phase III, open, non-randomized, non-comparative, multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	2 treatments, 7 days apart; if treatment failure at 3-month follow-up, another treatment cycle was given Methyl aminolevulinate cream applied 3 h before illumination	102 26-91 (64) Type I: 29 (28%) Type II: 46 (45%) Type ≥III: 27 (27%)	66M, 36F 102 C

Table 17: Table of Studies in the ISS

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 I							
PC T101/97 June 1997 to October 1998	Norway Warloe	Nodular BCC	Phase I-II, open, single-center PK study	Each patient received 3 concentrations of Methyl aminolevulinate cream, 16 mg/g, 80 mg/g, and 160 or 168 mg/g, for either 3 or 18 h. Lesion biopsy was taken to determine penetration depth of active ingredient. Lesion then illuminated with light dose of 75 J/cm^2	Single treatment	16 3 hours: mean 67 years 18 hours: mean 72 years Fitzpatrick skin type not assessed	11 M, 5 F 16 U
Dose-Ranging, Phase II							
PC T203/98 ongoing Reports Initial – January 2001 12 m – June 2001 24 m – June 2002 Final (36 m) expected Feb 2003	Norway, Sweden, Finland, Switzerland, Netherlands, France Basset-Séguin (France)	Primary BCC	Phase I-II, open, randomized, parallel-group, multicenter	Methyl aminolevulinate cream 168 mg/g for 1, 3, 5, or 18 h, with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	1 or 2 treatments, cream on the skin 1, 3, 5, or 18 hours before illumination	141 34 for 1 h treatment 36 for 3 h treatment 35 for 5 h treatment 36 for 18 h treatment 33-93 (64) Fitzpatrick skin type not assessed	76 M, 65 F 141 C
Studies in Actinic Keratosis							
Placebo-Controlled, Phase III							
PC T306/99 Jun 2000 to Feb 2001 Final	US Pariser	AK Thin to moderate AK lesions of the face and scalp 4 to 10 lesions per patient	Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter	Two treatments, 7 days apart Methyl aminolevulinate cream 168 mg/g or placebo for 3 h, with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	Two treatments, 7 days apart	80 31-84 (65) Methyl aminolevulinate cream: 31-84 (64) Placebo: 39-84 (67)	70 M, 10 F 80 C Methyl aminolevulinate cream: 36 M, 6 F Placebo: 34 M, 4 F

Table 17: Table of Studies in the ISS

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)
PC T305/99 Mar 2000 to Dec 2000 Final	Australia Foley	Thin to moderate AK lesions of the face and scalp Unlimited number of lesions	Phase III, randomized, parallel-group, multicenter, comparative vs. cryotherapy and placebo Open for Methyl aminolevulinate cream vs cryotherapy; double-blind for Methyl aminolevulinate cream vs. placebo	Two treatments, 7 days apart Methyl aminolevulinate cream 168 mg/g or placebo for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm) Cryotherapy: liquid nitrogen spray; 1 freeze-thaw cycle	Two treatments, 7 days apart (for Methyl aminolevulinate cream) 1 treatment (for cryotherapy)	200 33-89 (64) Methyl aminolevulinate cream: 33-86 (64) Placebo: 49-89 (66) Cryo: 38-86 (65)	119 M, 81 F 200 C Methyl aminolevulinate cream: 49 M, 39 F Placebo: 16 M, 7 F Cryo: 54 M, 35 F
PC T302/99 Jun 1999 to Jan 2000 Final	Denmark, Norway Bjerring (Denmark)	AK Unlimited number of lesions	Phase III, stratified, randomized, double-blind, placebo-controlled, parallel-group, multicenter	Methyl aminolevulinate cream 168 mg/g or placebo for 3 h, with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	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)	25 M, 14F 39 C
Active-Controlled, Phase III							
PC T301/99 Apr 1999 to Nov 1999 Final	Switzerland, Germany, Austria, Italy, Netherlands Braathen (Switzerland)	AK 1-10 lesions	Phase III, open, randomized, parallel-group, multicenter, comparative vs. cryotherapy	Methyl aminolevulinate cream: 168 mg/g or placebo for 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm) Cryotherapy: standard liquid nitrogen spray Two freeze thaw cycles (single session)	Methyl aminolevulinate cream: Single treatment for lesions on face and scalp Second treatment after 1 week for lesions at other locations Cryotherapy: 2 cycles in a single session Follow-up 3 months after treatment	202 42-89 (71) Methyl aminolevulinate cream: 42-88 (71) Cryo: 45-89 (72)	124 M, 78 F 202 C Methyl aminolevulinate cream: 66 M, 36 F Cryo: 58 M, 42 F
PC T311/01 ongoing	Sweden Tarstedt	AK 1-10 mild to moderate lesions on face or scalp	Phase III, open, randomized, parallel-group, , multicenter	Methyl aminolevulinate cream 168 mg/g for 3 h, with light dose of 37 J/cm^2 (wavelength 620 to 650 nm)	1 treatment; second treatment 3 months after first, if non-CR or 2 treatments, 7 days apart	Not available	Not available

Table 17: Table of Studies in the ISS

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)
Uncontrolled, Phase I and Phase II							
PC T204/98 Nov 1998 to May 2000 Final	Norway Christensen	AK Unlimited number of lesions	Phase II, open, randomized, within-patient controlled, single-center, comparative vs. Efudix®	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 5 J/cm^2 (wavelength 420 nm) Efudix® applied twice daily for 3 weeks Methyl aminolevulinate cream repeated at 3 months if non-CR; light dose of 75 J/cm^2 (wavelength 570-670 nm)	Methyl aminolevulinate cream: 1 treatment, second treatment at 3 months after first, if non-CR Efudix®: 3 weeks	12 59-82 (72)	10 M, 2 F 12 C
PC T202/98 Aug 1998 to Mar 2000 Final and 12-month follow-up report	Switzerland, Norway, Netherlands, Sweden, Finland, Germany Braathen (Switzerland)	AK Unlimited number of lesions	Phase I/II, open, randomized, parallel-group, multicenter, dose-finding	Methyl aminolevulinate cream 80 or 168 mg/g for 1 or 3 h with light dose of 75 J/cm^2 (wavelength 570 to 670 nm)	1 treatment; second treatment at 2 or 3 months after first, if non-CR	112 43-91 (73) 1 h, 80 mg/g: 55-91 (75) 1 h, 168 mg/g: 43-84 (70) 3 h, 80 mg/g: 58-90 (74) 3 h, 168 mg/g: 46-85 (73)	63 M, 49 F 112 C 1 h, 80 mg/g: 17 M, 8 F 1 h, 168 mg/g: 12 M, 16 F 3 h, 80 mg/g: 16 M, 13 F 3 h, 168 mg/g: 18 M, 12 F
Studies in BCC and AK							
Phase II							
PC T206/98 Sep 1998 to Apr 1999 Final	Norway Giercksky	Superficial BCC, at least 3 lesions, or AK, at least 4 moderately thick lesions	Phase I-II, randomized, double-blind, placebo-controlled, single-center	Methyl aminolevulinate cream 16, 80, or 168 mg/g or placebo cream for 28 h with light dose of 75 J/cm^2 (wavelength 570-670 nm)	Single treatment	15 58-89 (76)	10 M, 5 F 15 U
Studies in Other Indications							
PC T001/97 Sep 1997 to Dec 1999 Interim report	Norway Warloe	BCC, AK, and other non-melanoma skin cancers Unlimited number of lesions	Prospective, open, single-center compassionate use during Phase I-III studies	Methyl aminolevulinate cream 168 mg/g with light dose of 25 to 200 J/cm^2	Varied. 85% the lesions had 1 treatment, but others had up to 5 treatments.	1012 to date. 14-98 (68)	Not stated

Table 17: Table of Studies in the ISS

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)
PC T208/98 Jul 1999 to Feb 2001 Final	Denmark Wulf	Transplant recipients, using immuno-suppresive medication, with AK. 4-20 lesions per patient.	Phase II, open, randomized, within-patient untreated controlled, 2-center	Methyl aminolevulinate cream 168 mg/g for 3 h with light dose of 75 J/cm^2 (wavelength 570-670 nm)	Single treatment at study start. In a subgroup of patients, 1 additional cycle, comprising two treatment sessions 1 week apart, at Month 4.	27 32-75 (57)	17 M, 10 F 27 C
PC T211/00 ongoing	Germany Fritsch	BCC Photodynamic diagnosis of at least 10 superficial and nodular lesions, eligible for surgical excision	Phase II, within-patient controlled, dose-ranging	Methyl aminolevulinate cream 168 mg/g for 3, 5 and 24 h with light dose of 5 J/cm^2 (wavelength 370-400 nm)	24-hour application	Not available	Not available
PC T309/00 ongoing	Scotland Morton	Bowen's disease	Phase III, randomized, placebo- and active-controlled, multicenter	Methyl aminolevulinate cream 168 mg/g or placebo for 3 h with light dose of 75 J/cm^2 (wavelength 570-670 nm)	Methyl aminolevulinate cream and placebo: 2 treatments, 7 days apart; another treatment cycle if non-CR Cryotherapy: Single treatment; second treatment if non-CR 5-Fluorouracil: Cream applied for 4 weeks; second 4-week treatment if non-CR	Not available	Not available
Studies in Healthy Volunteers							
PC T107/01 Apr 2001 Final	US Maibach	Healthy subjects	Phase I/II, double-blind, within-subject vehicle–controlled, randomized, single-center acute skin irritancy study	Methyl aminolevulinate cream 168 mg/g and placebo for 24 h with no light therapy	Cream on the skin for 24 hours	12 41-80 (61)	4 M, 8 F 9 C, 2 NC, 1 U

Table 17: Table of Studies in the ISS

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)
PC T108/01 Jun to Jul 2001 Final	US Maibach	Healthy subjects	Phase I/II, double-blind, within-subject vehicle-controlled, randomized, single-center cumulative skin irritancy and sensitization study	Methyl aminolevulinate cream 168 mg/g and placebo with no light therapy	5 days weekly for 2 weeks. 3 weeks later, 48–hour cream application, and 3 weeks thereafter a 48-hour re-test.	25 32-83 (58)	12M, 13F 24 C, 1 U
PC T212/00 ongoing	Germany Szeimies	Healthy subjects	Phase II, randomized, within-subject controlled	Methyl aminolevulinate cream 168 mg/g or cream containing 20% ALA for 5 h with light dose of 75 J/cm^2 (wavelength 580-740 nm)	Up to 24-hour application	Not available	Not available
PC T214/01 Feb to Jun 2002 Final	Norway Warloe	Healthy subjects	Phase II, double-blind, within-subject controlled pharmacokinetic study	Phase I: Methyl aminolevulinate cream 168 mg/g and placebo cream for 3 h Phase II and III: Methyl aminolevulinate cream 168 mg/g and placebo cream for 3 h with light dose of 50 J/cm^2 (wavelength 570-670 nm)	No treatment. 3-hour application in all 3 phases.	16 20-30 (25) Type I: 1 (6%) Type II: 6 (38%) Type III: 9 (56%)	14M, 2F 16 C

5 CLINICAL PHARMACOLOGY

5.1 Photoactive Porphyrin Formation

MAL cream contains methyl aminolevulinate, which is an ester of 5-aminolevulinic acid (5-ALA), an endogenous early precursor in the biosynthesis of heme (see Figure 8). 5-ALA is formed in the mitochondria from glycine and succinyl coenzyme A by the enzyme 5-aminolevulinic synthase.[32] Two molecules of 5-ALA are then condensed to form the first intermediate, porphobilinogen. In mammals, the heme synthesis pathway occurs in the mitochondria and in the cytosol and takes place in all nucleated cells.

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

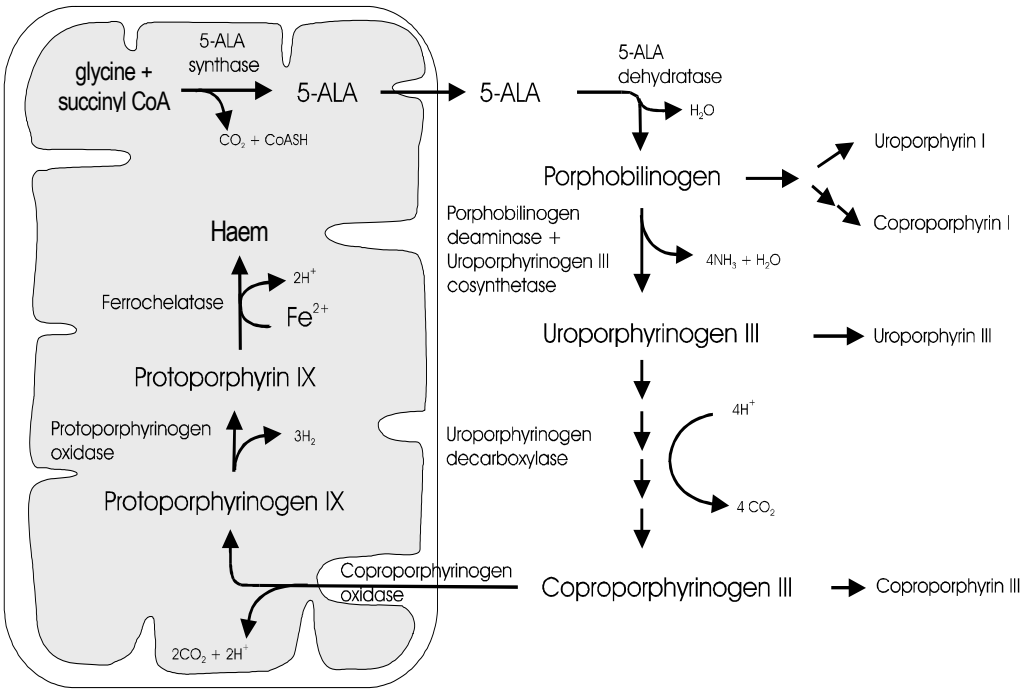


Figure 8: Biosynthetic Pathway of Heme in the Cell Mitochondria

The intracellular accumulation of PAPs such as PpIX can be measured directly by virtue of their fluorescence. The rate of 5-ALA/5-ALA ester-induced porphyrin synthesis has

been shown to be higher in malignant and premalignant cells and tissues than in their normal counterparts.[31] Furthermore, fluorescence was shown to be more selectively localized in tumor cells after application of methyl aminolevulinate than after 5-ALA treatment.[33] This greater selectivity is a desirable property with regard to both efficacy and safety since normal skin and other tissues are unaffected.

These observed differences in selectivity are not fully understood and can only be explained partly; they may be due to differences in tissue penetration and distribution, in cellular uptake mechanism, and activation of the heme synthesis enzymes. Furthermore, a topically applied compound has to penetrate the tissue and diffuse through epidermal layers. A more lipophilic agent than 5-ALA is likely to penetrate deeper. It has been shown that 5-ALA-induced PpIX formation is often limited to superficial tissue.[34] Using the partition coefficient as a measure for lipophilicity, it has been shown that methyl aminolevulinate seems to penetrate twice as efficiently as 5-ALA into the skin lesions.[35]

There is limited knowledge about the cellular uptake mechanism for methyl aminolevulinate. However, methyl aminolevulinate seems to have a different uptake mechanism from 5-ALA, and this can be one explanation for the difference in selectivity. In contrast to uptake of 5-ALA, uptake of methyl aminolevulinate into a human colon adenocarcinoma cell line has been shown to involve transporters of non-polar amino acids, and it does not seem to be taken up by system BETA transporters.[36,37]

In summary, methyl aminolevulinate is selectively absorbed by the lesion and is subsequently converted to PAPs in the mitochondria of proliferating epithelial cells. PAPs are activated by light of the appropriate wavelength. For MAL-PDT, red light in the range 570 to 670 nm is used, which is within the visual spectrum. Upon activation of light in the presence of oxygen, singlet oxygen is formed which causes damage to intracellular compartments, in particular the mitochondria, leading to cell death possibly by apoptosis.[38] In addition, inhibition of mitochondrial dehydrogenase, reduced respiration, and mitochondrial swelling have been reported.

5.2 Systemic Absorption

An *in vitro* study showed that human skin had a much lower permeability for ^{14}C-methyl aminolevulinate than rat skin. The systemic absorption through human skin was only 0.26% of the applied dose after a 24-hour application. The penetration was linear after a lag period of 1.6 hours. The systemic absorption through human skin of only 0.26% of the applied dose after a 24-hour application means that if a very large human dose of 1680 mg (10 g methyl aminolevulinate cream) were used, only 4.37 mg would be absorbed systemically after a 24-hour application time. However, in a clinical setting, an application time of only 3 hours is used. Therefore, assuming a 1.6-hour lag phase, 4.37 mg x (3-1.6)/24 = 0.250 mg = 250 μg of the large human dose of 1.68 g methyl aminolevulinate (from a topically applied dose of 10 g of methyl aminolevulinate cream) will be absorbed systemically. This amount is considered to be negligible and is consistent with the observations described in the preclinical safety section (see Section

3), including that no systemic toxicity has been observed after single and repeated topical application of cream MAL cream.

The pharmacokinetics of methyl aminolevulinate after IV or oral administration was not investigated in humans, because this type of study was not considered appropriate for a topical product such as methyl aminolevulinate cream 168 mg/g.

Negligible systemic exposure is also expected because of the nature of the lesions being treated. Both AK and BCC lesions are tumors of the epidermis and the basement membrane is generally intact.[39,40] Since methyl aminolevulinate cream 168 mg/g is applied only to the lesion and a small rim of surrounding skin, it is unlikely that substantial quantities of drug penetrate the basement membrane and gain access to the vascular dermis and hence the systemic circulation.

5.3 Selection of Dose Regimen for Pivotal Studies

Treatment of BCC with MAL-PDT is comprised of several components. The dose of MAL-PDT is dependent on the concentration of MAL cream, the length of time that the cream is applied to the skin and the light dose (ie, fluence) delivered in the PDT. The optimal dose of MAL and light as well as application time were ascertained in Phase I and II studies, described below.

5.3.1 Concentration and Application Time of MAL Cream

The following factors were taken into account in selecting the optimum concentration of cream and the duration of its application prior to illumination:

- Local pharmacokinetics, including depth and surface fluorescence of the fluorescent photoactive porphyrins in lesions and normal surrounding skin after application of cream in various concentrations of methyl aminolevulinate hydrochloride as demonstrated in Studies 101/97 and 206/98. Fluorescence depth, intensity of surface fluorescence, and ratio of fluorescence in diseased/non-diseased tissue (selectivity) were all studied as surrogate markers of efficacy;
- The response rate of BCC lesions and the safety of patients in Study 203/98 in which MAL cream was applied for different durations prior to illumination.

In addition, patient convenience and acceptability were taken into account, so that the duration of application was to be the minimum consistent with the best outcomes to be obtained in the clinical trials.

5.3.2 Study 101/97

An open, exploratory, (Phase I/II) study of P-1202 (MAL) 160 mg/g cream in patients with nodular basal cell carcinoma

Objectives, Design, and Methods

The primary objective was to determine the optimal MAL cream concentration and duration of application for treating nodular BCC lesions based on the formation of PAPs in the lesion. Six dosage regimens were tested consisting of MAL cream of 3 different strengths (16, 80, or 160 mg/g methyl aminolevulinate) each applied using 2 different application times (3 h or 18 h). Secondary objectives were to determine the safety, tolerability and response rate.

The study was conducted at a single center, the Norwegian Radium Hospital, Oslo. An open-label study design was employed in which lesions in patients fulfilling the inclusion criteria were identified and then randomized to treatment with one of the 3 concentrations of cream. Patients were either treated for 3 h or 18 h so that all lesions within any patient were treated with the same application time. The primary efficacy parameter was the distribution of PAP fluorescence in biopsies of verified nodular BCC lesions taken at the end of the period of application prior to photoactivation. Fluorescence of PAP across the full thickness of each lesion was measured using quantitative fluorescence microscopy with a highly light sensitive charge-coupled device camera, as exemplified in Figure 9 below. Despite the open study design, the pathologist performing microscopic fluorescence photometry was blinded to treatment.

Figure 9: Measurement of Penetration Depth of MAL in Nodular BCC

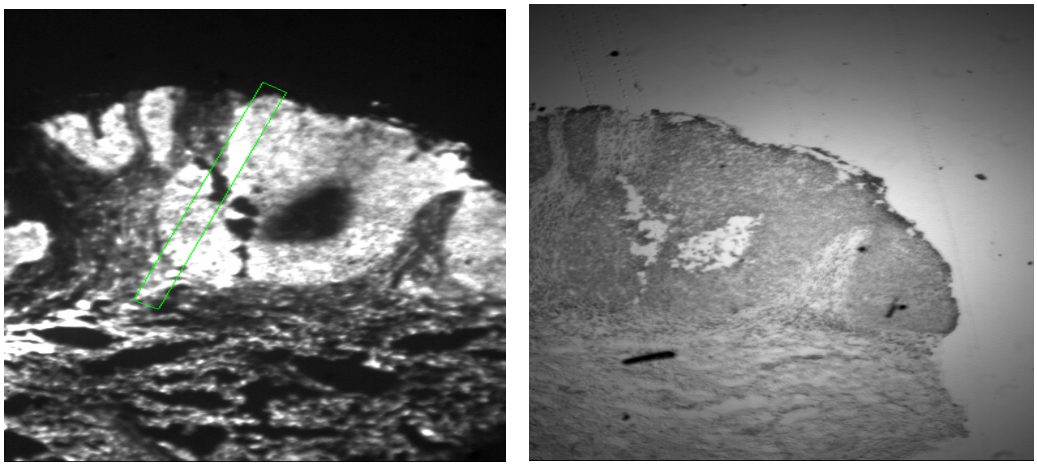


Figure 9: Measurement of penetration depth of MAL in nodular BCC. MAL cream was applied to BCC lesions and histological section of the BCC was examined by fluorescence microscopy (left image) and regular HE staining (right image). The left panel is a black and white fluorescence image of a nodular BCC. Fluorescence appears as white. Right panel is the same section with HE staining to show the histological border of the BCC lesion.

In total, 18 patients with 32 verified nodular BCC lesions were treated, 5 or 6 lesions for each of the 6 dosage regimens. A further 11 lesions that were determined not to be nodular BCC were excluded from evaluation. It was intended that each lesion within a patient would be treated with a different concentration of MAL cream but to complete the study in a timely and balanced manner, 3 patients had more than 1 lesion treated with the same concentration.

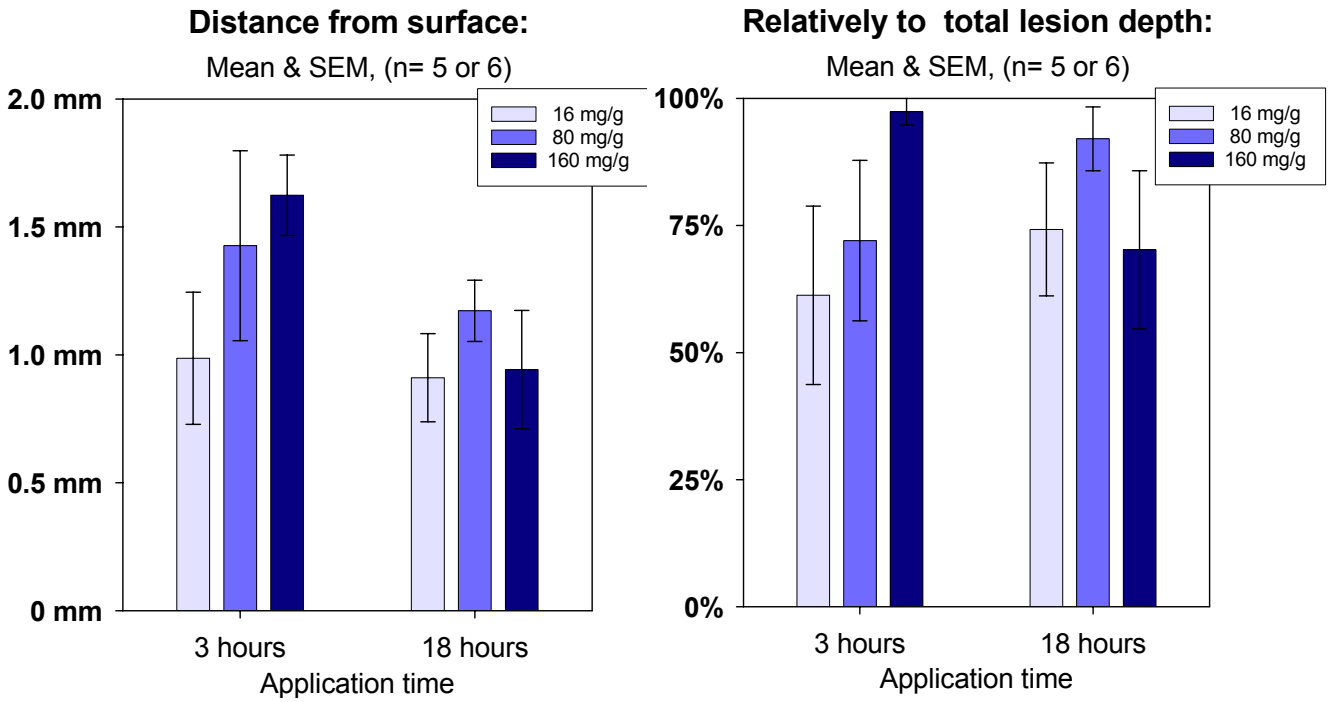
Dose and Time-Dependency of Fluorescence in Nodular BCC

The concentration of methyl aminolevulinate in cream was positively associated with increased depth of penetration of PAP fluorescence (Figure 10, left panel). This was seen most consistently with the 3-h application time. The depths of fluorescence (mean $\pm$ standard deviation, SD) were 0.7 $\pm$ 0.4, 1.0 $\pm$ 0.6, and 1.3 $\pm$ 0.5 mm for the 16, 80, and 160 mg/g concentrations respectively. Depth of penetration was not increased with the longer (18-h) application time and the concentration-response relationship was more variable (depth of penetration 0.5 $\pm$ 0.4, 0.96 $\pm$ 0.2 and 0.83 $\pm$ 0.6 mm). In view of the greater depth of the lesions treated for 3 h, the relative depth of penetration (depth of fluorescence/depth of lesion) was also determined. Optimum penetration (98% $\pm$ 4%; >90% in all lesions) was only achieved by the 160-mg/g concentration applied for 3 h (Figure 10, right panel).

Selectivity for Lesions

Selectivity was assessed by the pathologist who examined normal skin adjacent to the lesion for PAP fluorescence following application of MAL cream in accordance with the randomization schedule. Only 1 of 16 lesions treated with a 3-h application time was reported as showing ‘much’ fluorescence in normal skin. Fluorescence in normal skin was generally higher after an 18 h application time for all 3 cream strengths; 12 of 16 lesions were reported as showing ‘much’ fluorescence.

Figure 10: Depth of PAP Fluorescence in Relation to MAL Cream Concentration and Application Time



5.3.3 Study 206/98

A Pharmacokinetic Study of Protoporphyrin IX formation in Patients with Actinic Keratosis and Basal Cell Carcinoma after Topical Application of P-1202 (MAL) Cream.

Objectives, Design, and Methods

The primary objective of Study 206/98 was to compare the fluorescence of PAP in superficial BCC and AK at different time intervals after topical application of methyl aminolevulinate cream containing concentrations of 0 mg/g (placebo, AK only), 16 mg/g, 80 mg/g, or 168 mg/g methyl aminolevulinate. Secondary objectives were to determine other pharmacokinetic parameters, response rate, and safety. In addition, PAP fluorescence was measured in normal skin and in treated normal skin.

This was a prospective, double-blind, randomized, controlled study performed at a single center. Seven consenting adult patients with at least 3 superficial BCC lesions and 8 patients with a minimum of 4 moderately thick AK lesions were recruited. The 3 BCC lesions per patient were randomized to be treated with one of the 3 treatments so that each patient received each treatment on a different lesion:

- Methyl aminolevulinate 16 mg/g Cream for 28 hours,
- Methyl aminolevulinate 80 mg/g Cream for 28 hours,
- Methyl aminolevulinate 168 mg/g Cream for 28 hours.

The 4 AK lesions per patient were randomized for treatment with 1 of the 3 cream strengths or placebo.

The lesions were prepared before the application of the cream so that penetration of cream to the lesion would not be compromised. To standardize the preparation procedures, a guideline was provided, which described how crusts were to be removed by a small curette and that the surface was to be scraped gently in order to roughen the surface. This procedure is identical to that used in the Phase III trials.

After 28 hours, the dressing and excess cream were removed and lesions were illuminated with non-coherent light (570 to 670 nm) with a fluence of 75 J/cm^2. Fluorescence in lesions and surrounding skin was measured with optical fiber point monitoring before cream application, subsequently at frequent intervals for 28 h during cream application, 1 h after illumination (at 29 h) and at 48 h.

Dose and Time-Dependency of Fluorescence in Lesions

Table 18 shows fluorescence measurements in the AK lesion at various times after cream application. Fluorescence measurements 1 hour after application were similar to those prior to application (data not shown). At 3 hours there was a clear increase in PAP fluorescence intensity in the lesions compared with levels at 1 hour or those with placebo. After log transformation of the data, the 95% CIs for the difference between fluorescence compared with placebo showed a statistically significant increase at 3 hours and 5 hours for the highest concentration (168 mg/g) cream. A significant increase in fluorescence

was not shown for 16 mg/g and 80 mg/g applied for 3 and 5 hours. The 1-hour application was not sufficient to show significance for any of the 3 methyl aminolevulinate cream concentrations.

Table 18: PAP Fluorescence in Treated AK Lesions by Cream Concentration and Time of Measurement (Study 206/98)

Concentration of methyl aminolevulinate cream	Number of Lesions	PAP Fluorescence in Lesion Mean ± SD			
		1 hour	3 hours	5 hours	21 hours
0 mg/g	8	30.3 ± 5.7	26.7 ± 5.1	26.3 ± 5.4	24.2 ± 3.5
16 mg/g	8	37.9 ± 9.9	59.9 ± 47.0	78.1 ± 77.0	92.0 ± 59.0
80 mg/g	8	37.5 ± 15.8	56.8 ± 36.6	68.1 ± 55.5	116.8 ± 95.1
168 mg/g	8	38.1 ± 12.3	61.4 ± 28.4	78.2 ± 42.8	113.1± 60.5

Data source: Table 7A in 206/98 study report.

Plots of median PAP fluorescence versus time in AK lesions showed dose-related increases from 3 hours onward, reaching a plateau at about 9 hours for the higher concentrations (data not shown). Although the results showed variation and mean results failed to show a significant dose-response relationship, higher doses generally achieved greater concentrations of PAP in lesions. Furthermore, only the PAP fluorescence intensity after the 168-mg/g strength was significantly different from that after placebo at 3 hours and 5 hours. The optimum duration of application of methyl aminolevulinate cream cannot be determined precisely but it would appear to lie between 3 hours and 9 hours. There seemed to be no additional benefit to be gained from longer application times.

Table 19 summarizes fluorescence measurements in the BCC lesions. Fluorescence measurements at 1 hour after application were similar to those prior to application (data not shown). As with the AK lesions, the data were highly variable. However, all 3 cream concentrations resulted in clear increases in PAP fluorescence in BCC lesions with time (Table 19 and Figure 11).

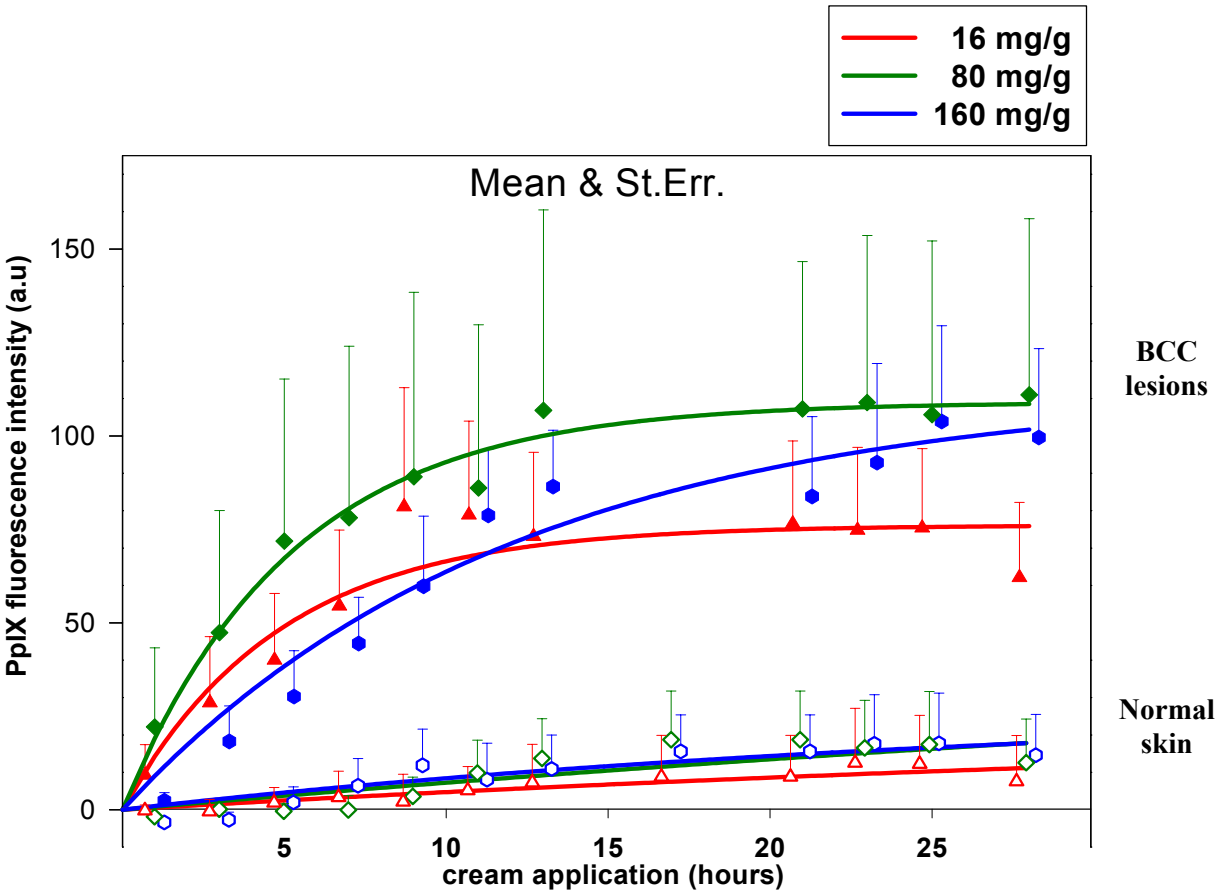
Table 19: PAP Fluorescence in Treated BCC Lesions by Cream Concentration and Time of Measurement (Study 206/98)

Concentration of methyl aminolevulinate cream	Number of Lesions	PAP Fluorescence in Lesion (Mean ± SD)			
		1 hour	3 hours	5 hours	21 hours
16 mg/g	6	41.6 ± 16.9	58.1 ± 39.4	69.6 ± 40.5	98.6 ± 47.0
80 mg/g	6	44.6 ± 21.8	72.6 ± 60.1	98.5 ± 87.6	154.3 ± 111.8
168 mg/g	6	31.9 ± 7.7	45.9 ± 22.1	59.5 ± 31.0	113.7 ± 50.0

Data source: Table 9A in 206/98 study report.

Inspection of plots of mean PAP fluorescence versus time (Figure 11) showed that the increase in fluorescence was rapid, with about a 2-fold increase after a 3-hour application, reaching a plateau by 10 to 12 hours.

Figure 11: Fluorescence Intensity in BCC Lesions and Normal Skin



Selectivity for Lesions

Table 20 summarizes the results for PAP fluorescence around AK lesions. In normal treated skin surrounding the AK lesions, only a minor build-up of PAP fluorescence (9% to 17%) was observed after treatment with 80 mg/g and 168 mg/g during the first 5 hours. However, after 21 hours of application, PAP fluorescence increased to 74% of the untreated level for 80 mg/kg and 143% of the untreated level for 168 mg/g. Comparing the different methyl aminolevulinate cream concentrations and placebo cream, significantly higher levels of PAP fluorescence were observed from 3 to 21 hours with different methyl aminolevulinate cream concentrations compared to placebo, and for methyl aminolevulinate cream 168 mg/g compared to 16 mg/g after 21-hour application.

Table 20: PAP Fluorescence in Normal Skin Around AK Lesions by Cream Concentration and Time of Measurement (Study 206/98)

Concentration of methyl aminolevulinate cream	Number of lesions	PAP Fluorescence in Normal Treated Skin Around Lesion Mean ± SD			
		1 hour	3 hours	5 hours	21 hours
0 mg/g	8	31.0 ± 5.2	28.6 ± 4.3	27.8 ± 4.7	28.0 ± 5.0
16 mg/g	8	34.8 ± 5.8	34.1 ± 5.6	35.3 ± 5.3	34.1 ± 6.5
80 mg/g	8	29.0 ± 3.9	31.5 ± 5.2	32.8 ± 8.0	50.5 ± 12.0
168 mg/g	8	27.3 ± 3.1	30.2 ± 5.5	35.6 ± 12.4	66.5 ± 43.5

Data source: Tables 7B in 206/98 study report.

As shown in Table 21, results were qualitatively similar for all cream concentrations in normal treated skin surrounding the BCC lesions with no increase of PAP fluorescence levels observed after 3 and 5 hours application time compared to 1 hour. After 21 hours of cream application, an increase in PAP fluorescence level of about 65% compared to 1 hour was observed for all 3 concentrations of methyl aminolevulinate cream.

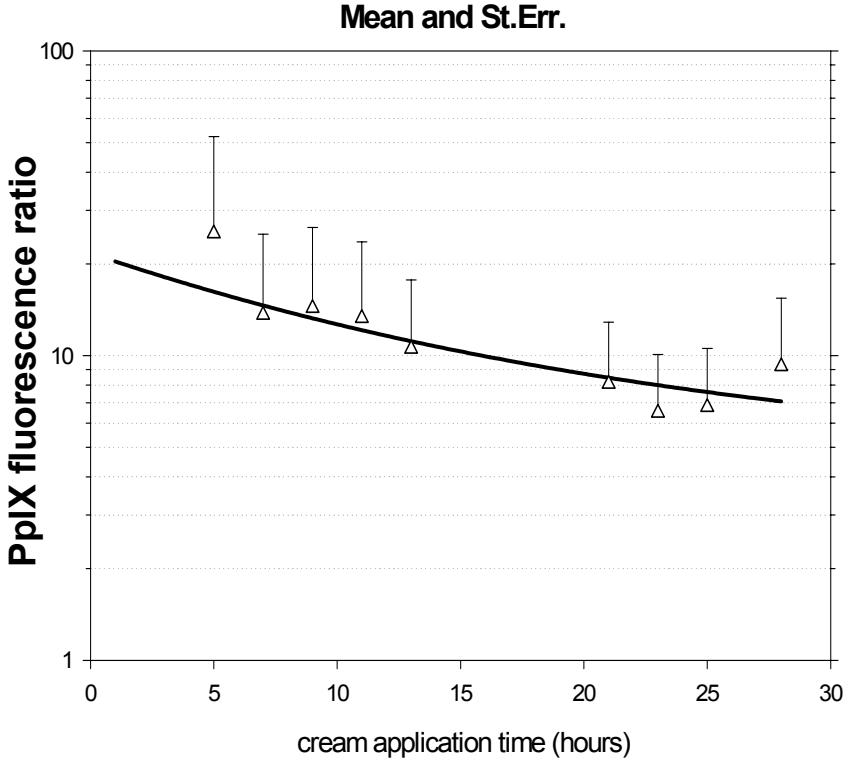
Table 21: PAP Fluorescence in Skin Around BCC Lesions by Cream Concentration and Time of Measurement (Study 206/98)

Concentration of methyl aminolevulinate cream	Number of Lesions	PAP Fluorescence in Normal Treated Skin around Lesion (Mean ± SD)			
		1 hour	3 hours	5 hours	21 hours
16 mg/g	6	34.3 ±6.6	37.4 ±10.1	40.4 ± 13.5	55.9 ± 45.3
80 mg/g	6	34.4 ±9.5	34.2 ± 5.7	35.3 ± 5.7	55.0 ± 32.2
168 mg/g	6	28.4 ±5.2	29.3 ± 7.4	33.2 ± 11.9	48.2 ± 26.2

Data source: Table 9B in 206/98 study report.

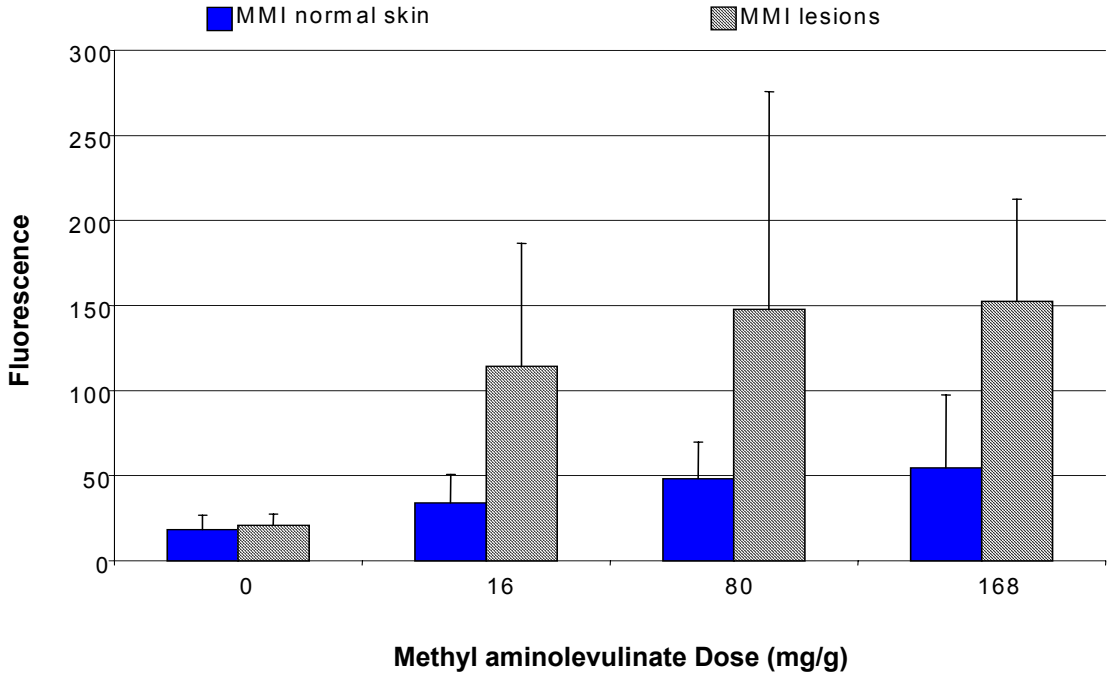
Examining the ratio between PAP fluorescence intensity in BCC lesions and normal skin (Figure 12), the PAP fluorescence data show that methyl aminolevulinate is selectively absorbed by the lesion compared to normal skin and at early time points there is 10 to 20-fold higher PAP fluorescence in the BCC lesions compared to treated normal skin.

Figure 12: Fluorescence Ratio of BCC Lesion Versus Normal Skin in Relation to Application time



Non-parametric statistical tests were performed on the MMI (maximum-minimum ranges) for each data set. Figure 13 shows the results for combined AK and BCC lesions and surrounding normal skin. Despite the variation in the responses within each lesion group, PAP accumulation in lesions in general was much higher than in normal skin. When subjected to non-parametric analysis, statistically significant differences were found between fluorescence levels in normal skin versus in lesions: P=0.0088 for the 16 mg/g group; P=0.0346 for the 80 mg/g group; P=0.0001 for the 168 mg/g group.

Figure 13: Fluorescence in PAP Lesions and Normal Skin (Study 206/98)



Photobleaching

There was no apparent decline in fluorescence from the time that cream was applied until photoactivation with 75 J/cm^2 at 28 hours (data not shown). However, within 1 hour after illumination, levels of fluorescence had fallen to baseline. It is evident that this process, known as photobleaching, is complete after photoactivation and levels of fluorescence at 48 hours also were similar to those at baseline confirming that no further accumulation of PAP had occurred subsequent to photoactivation (data not shown). This is consistent with the mechanism of action of MAL-PDT and reassuring with respect to safety.

5.3.4 Study 203/98

An open exploratory (Phase I/II) study of P-1202 (MAL) 160 mg/g cream in patients with primary basal cell carcinoma.

Objectives, Design, and Methods

The primary objective was to determine the complete response rate in patients with primary (non-recurrent) BCC after 1 or 2 treatments with topical MAL-PDT using 4 different cream application times. The cream concentration was fixed at 168 mg/g, since that was the only concentration shown to give adequate depth penetration to treat nodular BCC effectively (Study 101/97). Secondary objectives were to determine the complete response rate after 1 treatment with topical MAL using different application times, to determine the cosmetic outcome in lesions with complete response, to evaluate safety, and to evaluate the recurrence rate of lesions with complete response during

36 months of follow up. This summary addresses follow-up to 24 months after the last MAL-PDT.

The study was a prospective, open, randomized, parallel group multicenter study conducted in 8 European sites. Consenting adult patients with at least 1 previously untreated, superficial or nodular BCC and skin type I, II, or III (Fitzpatrick classification) were recruited. The study comprised a screening period of up to 2 weeks, 1 or 2 treatments with an interval of 2 to 3 months, and a follow-up period. Lesions were diagnosed clinically by a specialist dermatologist and confirmed using histology or cytology.

After preparation, MAL cream (168 mg/g) was applied for 1, 3, 5, or 18 h in accordance with the randomization schedule for each center followed by illumination with non-coherent light of wavelength 570-670 nm and fluence 75 J/cm^2. Evaluation of lesion response was performed at 2 and 3 months. In patients with incomplete responses after 2 or 3 months, the treatment was repeated, and the response assessed after an additional 3-month period. Analyses of recurrence data collected at the 24-month assessment focused on results in all patients treated who had at least one lesion in complete response (CR).

The primary efficacy variable was changed during the study from Lesion Complete Response Rate to Patient Response Rate (the number of lesions with complete response divided by the total number of lesions for the individual patient) since it could not be established that different lesions within the same patient behaved independently. Confidence intervals (CI, 95%) for the mean Patient Response Rates for each application time were calculated. To test for differences in Patient Response Rates and Patient Recurrence Rates between treatment groups, an analysis of variance (ANOVA) was done with application time as a covariate. In addition, a multiple comparison using the Tukey's Studentized Range Test was performed to compare the Patient Response Rates between groups. New sample size calculations were performed to ensure that the power of the study was maintained. With an anticipated mean Patient Response Rate of 90% in the 18-h application group, the sample size was determined to detect differences in other groups if the response rate in these groups was 70%.

Disposition of Patients

In total, 146 patients were screened and randomized. Five withdrew consent before treatment and 6 patients (7 lesions) were excluded from efficacy analysis (withdrawal of consent after treatment, 2; missing response evaluation due to AEs, 2; lost to follow-up, 2). Thus, the efficacy population consisted of 135 patients with 253 lesions, and the safety population of 141 treated patients with 260 lesions.

Lesions

The number of lesions per patient is shown in Table 22. The 141 patients enrolled had 260 BCCs. The majority of patients had one BCC lesion; 35% had more than one; only 7% had more than 4 BCCs (maximum 10). The distribution of lesions in the 3 h group was somewhat different from the other groups in that fewer than half the patients (44%)

had only 1 lesion. Seventy-nine (205/260) percent of lesions were superficial; 21% (55/260) were nodular. Twenty-seven (70/260) percent of lesions were on the face or scalp; 63% (163/260) were on the neck or trunk; and 10% (27/260) were on an extremity.

Table 22: Number of Lesions per Patient

Study 203/98

Appli-cation Time	Number of Patients	Number of lesions N (%)								
		1	**2**	**3**	**4**	**5**	**6**	**8**	**10**	**Sum**
1 h	34	22 (65)	3 (9)	2 (6)	3 (9)	2 (6)	1 (3)	0 (0)	1 (3)	72
3 h	36	16 (44)	8 (22)	5 (14)	5 (14)	1 (3)	1 (3)	0 (0)	0 (0)	78
5 h	35	25 (71)	8 (23)	0 (0)	1 (3)	1 (3)	0 (0)	0 (0)	0 (0)	50
18 h	36	29 (81)	3 (8)	0 (0)	1 (3)	1 (3)	0 (0)	2 (6)	0 (0)	60
Total	**141**	**92 (65)**	**22 (16)**	**7 (5)**	**10 (7)**	**5 (4)**	**2 (1)**	**2 (1)**	**1 (1)**	**260**

Patient and Lesion Response

The mean Patient Response Rates (95% CIs) for all patients evaluated 3 months after their last MAL-PDT treatment (1 or 2 treatments as required) and after their first treatment only are shown in Table 23.

The analysis of variance showed no differences in the mean Patient Response Rates at 3 months between the treatment regimens after 1 or 2 treatments (P = 0.25). However, fewer patients required a second treatment for incomplete response at 3 months after a single 3 h application of MAL cream compared with after a single 1 h application (21% versus 47%). Similarly, there was no difference in the lesion response rates to the different application times if patients received a second treatment at 3 months if required but the number with incomplete responses after a single treatment and requiring a second course of treatment was highest in the l h treatment group. The proportions requiring re-treatment shown in Table 24 were 36%, 10%, 24%, and 12% in the 1 h, 3 h, 5 h and 18 h groups respectively.

Table 23: Patient and Lesion Response Rates

Study 203/98

Application Time	Mean (95% CI) Patient Response Rates			Mean Lesion Response Rates*		
	N	**First Treatment**	**Last Treatment****	**N**	**First Treatment**	**Last Treatment****
1 h	31	53% (36%-71%)	93% (84%-100%)	68	60%	96%
3 h	35	79% (65%-93%)	89% (78%-100%)	77	86%	92%
5 h	35	63% (47%-79%)	77% (63%-91%)	50	68%	80%
18 h	34	74% (58%-89%)	88% (77%-100%)	58	84%	93%

* Number of lesions with CR divided by total number of lesions. **Includes both 1 and 2 treatments
Data Source: Table VIII and Statistical Table 15 in the 203/98 Revised 3-Month Study Report.

Table 24: Number of PDT Treatments per Lesion

Study 203/98

Application Time	Number of Lesions	Number of treatments per lesion					
		1		2		3	
	n	n	%	N	%	n	%
1 h	72	46	64	25	35	1	1
3 h	78	70	90	8	10	0	0
5 h	50	38	76	12	24	0	0
18 h	60	53	88	7	12	0	0

Data Source: Table 13 in the 203/98 revised study report 08.12.2000.

A higher overall complete response rate (189/200 lesions, 95%) was observed for superficial lesions than for nodular lesions (41/53 lesions, 77%). A similar trend was noted after one treatment only (80% compared with 58%). The results indicate that a second treatment is frequently beneficial, particularly for nodular lesions.

Safety

Safety was evaluated after 3 months; a total of 590 separate AEs were reported by 135 of 141 patients. Almost all (571 AEs) were local, transient, mild or moderate expected phototoxic reactions including erythema, pain, edema and pruritus. The percentage of patients with at least one local AE in the 1 h, 3 h, 5 h and 18 h treatment groups were 97%, 89%, 97% and 100% respectively. However, there was a tendency towards a higher frequency and severity of local AEs in association with the longer application times. No patient in the 1 h and the 3 h treatment groups experienced a local AE graded severe, as compared with 5 patients in each of the 5 h and the 18 h groups. Two patients in the 18 h group discontinued the study due to pain during illumination. Three SAEs were reported; these were not treatment-related.

Recurrence

A total of 118 patients with 230 lesions that responded completely after one or two treatments were included in the recurrence evaluation 12 months after the last MAL-PDT. The overall Lesion Recurrence Rate was 10%, with no clear evidence of any relationship to duration of cream application, lesion description or location.

At 24 months, a total of 218 lesions in 112 patients, which had shown complete response, were evaluated for recurrence. The lesion recurrence rates were 21%, 18%, 13%, and 30% in the 1 h, 3 h, 5 h, and 18 h treatment groups respectively. One-way ANOVA of mean patient recurrence rates found no statistically significant difference among treatment groups.

In summary, the 4 application times investigated appeared, after 2 years of follow-up, to be similar in terms of recurrence, cosmetic outcome and safety.

Conclusions

- The mean Patient Response Rates in the whole study population after one or two treatments with MAL-PDT ranged from 77% to 93%. The mean Lesion Response Rates in the whole study population ranged from 80% to 96%.
- There was no evidence of any difference in response rates or recurrence rates between treatment groups after one or two treatments. However, mean Patient and Lesion Response Rates 3 months after one treatment only were lowest in the 1 h group and these patients were more likely to require a second treatment than those with longer application times. A greater proportion of nodular than superficial lesions required a second treatment to achieve a complete response.
- Cosmetic outcome 3 months after treatment was good in all groups at 3 months and tended to improve further with time shown in the 12- and 24-month assessments. Mild redness and hypopigmentation were the most frequently reported adverse outcomes; no cosmetic signs were rated as severe.
- The majority (96%) of AEs was local, mild or moderate phototoxic reactions. These tended to increase in frequency and severity with application time, particularly in the 5 h and 18 h groups.
- Since more than twice as many patients needed re-treatment in the 1-hour group than the 3-hour group (47% versus 21%) and the frequency and severity of local adverse events tended to increase with duration of application, 3 hours was chosen as the optimum application time for further clinical evaluation.

5.4 Conclusions on Dosage Selection for Pivotal Studies

Both of the local skin pharmacokinetic studies (Studies 101/97 and 206/98) indicate that a MAL cream concentration of 168 mg/g and an application time of between 3 and 10 hours are optimal. Lower concentrations were associated with less than optimal penetration and PAP generation throughout the depth of the lesions. A statistical analysis of the relative penetration depth found in Study 101/97 showed that 160 mg/g was significantly better than both 16 mg/g (P=0.03) and 80 mg/g (P=0.03). Study 206/98 showed that longer exposure was associated with a loss of lesion selectivity without any associated increase in PAP fluorescence. Based on the results of these 2 pharmacokinetic studies, the decision was taken to proceed to parallel group dose-response studies with clinical endpoints using the 168 mg/g concentration only, since that was the only concentration that results in adequately deep PAP generation for treatment of nodular BCC. In the clinical dose-response study, a series of application times was tested to assess the optimal balance between increasing photodynamic activity and the gradual loss of selectivity that is seen with increasing application times in the pharmacokinetic studies.

A cream application of 1-hour duration prior to PDT was associated with somewhat lower patient and lesion response rates than longer application times in Study 203/98. On the other hand, there was no indication that the 5-hour or 18-hour application times produced a higher response rate. It was later established that the recurrence rate was also not reduced by cream applications longer than 3 hours. The frequency of symptoms (eg, hypopigmentation, redness, and atrophy) did not change noticeably as the MAL cream application time increased, but phototoxicity was affected, with a slight increase in the severity of short-term symptoms with the long application times. As shown in the pharmacokinetic studies, this may be a reflection of the loss of selectivity with longer application times. In view of the pharmacokinetic, efficacy, and tolerability data and the acceptability to patients in terms of convenience, a treatment regimen of MAL 168 mg/g cream applied for 3 hours prior to photoactivation was selected for the pivotal trials.

It was also noted in the Phase II Study 203/98 that a greater proportion of nodular lesions required a second course of treatment at 3 months than superficial lesions. Therefore, it was decided to implement a second session of treatment after an interval of 1 week ie, a cycle of 2 sessions one week apart for all Phase III studies of nodular BCC. The interval of 1 week was supported by the fact that most phototoxic reactions were resolved in less than a week. For superficial lesions, 1 session was considered sufficient in the first instance but if retreatment were required at 3 months, a cycle of 2 sessions was to be administered.

The clinical studies with different illumination parameters and studies reported in the literature support the use of non-coherent light of wavelength 570-670 nm and a total fluence of 75 J/cm^2. These parameters were selected for use in all the pivotal trials.

5.5 Safety Pharmacology Studies in Healthy Volunteers (Skin Irritation and Sensitization)

5.5.1 Study 107/01

Study 107/01 was a double-blind, within-subject, vehicle-controlled, randomized, single-center safety study. The objective was to determine the acute irritancy potential of methyl aminolevulinate cream 168 mg/g and its vehicle. Twelve healthy subjects were included.

The method used was a modification of the Draize acute assay. Six patches, 3 with methyl aminolevulinate cream and 3 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, and another patch was covered with non-breathable, occlusive dressing. The cream was on the skin for 24 hours, and all sites were covered with a light occlusive cloth during this time to minimize possible phototoxic reactions. No illumination was performed. Skin irritation was assessed using the 6-point dermal response scale shown in Table 25.

Table 25: Skin Irritation Index

Score	Description of Response
0	Negative
0.5	Equivocal reaction
1	Erythema
2	Erythema and induration
3	Erythema, induration, and vesicles
4	Bullae

Data source: 107/01 study report.

Twelve subjects, 4 males and 8 females, were treated. The mean age of subjects was 61 years (range: 41 to 80 years). Nine subjects were Caucasian, 2 were Hispanic, and information on the race of 1 subject was missing. There were no AEs, and none of the patients discontinued the study prematurely.

Three of the 12 subjects (Subjects 1, 7, and 10) were scored as having an equivocal (0.5) response to 1 of the 6 combinations of cream and dressing to which they had been exposed. The results of this study of 24-hour acute irritancy did not reveal any acute irritation to methyl aminolevulinate cream or its vehicle cream in combination with either type of dressing. No AEs were reported.

5.5.2 Study 108/01

Study 108/01 was a double-blind, within-subject, vehicle-controlled, randomized, single-center safety study. The objective of Study 108/01 was to determine the relative

cumulative skin irritancy and sensitization potential of methyl aminolevulinate cream 168 mg/g and its vehicle. Twenty-five subjects were included.

The method used was based on the paper by Phillips et al.[41] and the relevant FDA guidance document.[42] Four patches, 2 with methyl aminolevulinate cream 168 mg/g and 2 with its vehicle cream were applied to normal healthy skin on the upper back of each subject. One patch in each group was covered with Tegaderm. Each test site was covered with a light occlusive cloth to minimize possible phototoxic reactions. Methyl aminolevulinate cream 168 mg/g and its vehicle cream were applied 5 days per week for a total of 14 days. The patches were applied for 23 hours on weekdays and 72 hours on weekends. A challenge was performed 2 weeks later by applying patches to new skin sites for 48 hours. The subjects returned to the center for dermal irritation scoring 48, 72, 96, and 120 hours later. A 48-hour re-test was conducted 3 weeks later, which included 8 of the original subjects. The cream was then applied for 48 hours; the site was evaluated for irritation 48 and 96 hours later.

An 8-point dermal response scale, shown in Table 26, was used to evaluate each test site for irritaiton. In addition, AEs were recorded.

Table 26: Dermal Response Score

Score	Description of Response
0	No evidence of any effect
1	Minimal erythema, barely perceptible
2	Definite 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 spreading beyond test site

Data source: 108/01 study report.

5.5.2.1 Cumulative Skin Irritancy

The mean value for the total cumulative irritation score for methyl aminolevulinate-treated sites was 4.36 (range: 0 to 19), and the score for vehicle-treated sites was 0.44 (range: 0 to 6). Corresponding scores for sites covered with Tegaderm dressing were 4.44 (range: 0 to 19) and 0.52 (range: 0 to 6).

The total cumulative irritation score (adjusted for the number of time points) was 0.48 (range: 0 to 2) for sites treated with methyl aminolevulinate and 0.05 (range: 0 to 0.7) for

sites treated with vehicle. Corresponding scores for sites covered with Tegaderm dressing were 0.49 (range: 0 to 2) versus 0.06 (range: 0 to 0.7).

The results suggest that there was cumulative mild and moderate irritancy in response to methyl aminolevulinate cream. However, no sign of irritancy (defined as readily visible erythema, minimal edema, or minimal papular [a dermal response score of 2]) was noted the first 4 days of continuous exposure. No cumulative irritancy could be detected in the vehicle group. Use of Tegaderm dressing did not affect the dermal response scores of the 25 subjects tested. No AEs were reported.

5.5.2.2 Skin Sensitization

Challenge applications at previously untested sites following the 2-week induction period resulted in 5 subjects in the methyl aminolevulinate group with scores of 2 or higher. Two of these subjects had a score of 5 and 1 subject had a score of 3. The same scores were obtained 3 weeks later, when a 48-hour re-test was performed on 8 subjects. No reactions occurred in the vehicle group, and the use of Tegaderm dressing had no effect on irritation. No AEs were reported.

Because 3 of 25 subjects had positive scores in the challenge and re-testing phases, a possible mild or moderate skin sensitization could not ruled out.

5.5.3 Study 110/03

5.5.3.1 Study Design

The study was designed according to the FDA "Guidance for Industry – Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products." The study was a double-blind, within-subject, vehicle-controlled, randomized, single center study in healthy volunteers, assessing sensitization by MAL cream and its vehicle and cross-sensitization to 5-aminolevulinic acid (ALA) and its vehicle. A total of 215 subjects were to be included in the study.

The study duration was 6 weeks. Following a screening period of 1 week, each subject received MAL cream and vehicle 3 times a week (Monday, Wednesday, Friday) for 3 weeks applied to separate sites on the back, resulting in 9 administrations over the period. On each application, the area was covered by an aluminum Finn Chamber, fixed in place by adhesive tape with a covering of opaque tape so that light exposure was minimized thereby preventing any phototoxic reaction which might confound the sensitization reaction. After the 3-week treatment period and a 2-week interval without applications, subjects were challenged with MAL cream, vehicle, ALA, and ALA-vehicle for 48 hours. Assessment of skin reactions was performed 48, 72, and 96 hours after start of the challenge cream application.

5.5.3.2 Criteria for evaluation

Skin reactions were classified into three categories: negative, equivocal and positive. The primary endpoint was the proportion of subjects in each of 3 categories of the contact

sensitization score (negative, equivocal, positive) at the end of the challenge phase at the end of the challenge phase.

Secondary endpoints were:

- The proportion of subjects with each of the eight-point erythema scores;
- The proportion of subjects with each of the clinical observation scores;
- The time for an erythema score of ≥2 to appear during the first week of the induction phase; and
- Adverse events.

5.5.3.3 Study Results

A total of 224 subjects were screened for the study, of which 156 were included and administered MAL/vehicle at least once. Due to the frequent irritancy occurring in the induction phase in the first subject cohort, the investigator and sponsor decided not to include more subjects. Therefore, remaining 68 subjects were screened but not entered into the study.

Of the 156 subjects that were included in the study, 98 proceeded to the challenge phase; 58 receiving both MAL and ALA, and a further 40 subjects receiving ALA only. Fifty-eight (58) subjects decided not to participate in the challenge phase and 40 subject only agreed to have the ALA application, all due to the irritation reactions seen with MAL in the induction phase. In addition 2 other subjects were withdrawn, one due to an unrelated SAE and one for other reasons.

Analysis of the sensitization potential by MAL 168 mg/g cream after prolonged exposure revealed that 52% of the subjects were regarded positive with respect to contact sensitization towards MAL, while 5% had an equivocal reaction and 41% did not develop sensitization (one subject was missing). The reactions were regarded as related to test drug since virtually no sensitization was observed to MAL vehicle (see Table 27 below).

Table 27: Contact Sensitization Score Following Application with MAL, MAL Vehicle, ALA, and ALA Vehicle

Compound	Number of subjects	Contact Sensitization Score							
		Missing		Negative		Equivocal		Positive	
	n	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

In 8 subjects, all of whom were judged sensitized, the patch became detached in the course of the challenge phase but the reactions developed before the patches were

detached and were therefore not regarded as being caused by photosensitization. No sensitization was observed towards the endogenous substance ALA or its vehicle.

All but one subject reacted with erythema on prolonged exposure (up to 3 weeks in the induction phase) to MAL. Again this was regarded as related to test drug since very little skin reaction was observed on sites exposed to vehicle. The earliest skin reactions of moderate severity (ie, more severe than 'slight patchy') occurred after 4 days of constant exposure to MAL cream. Also, the subjects that had a high irritation score (5 or 6) in the induction phase had a greater risk for sensitization in the challenge phase.

5.5.3.4 Conclusions

This study demonstrated a potential for sensitization towards MAL cream after prolonged exposure to the drug substance. Since 41% of the subjects were not sensitized, individual variation in the susceptibility is apparent. The reason for the high frequency of sensitization in this study is likely to be the extreme conditions of exposure to MAL cream. This is in contrast to clinical experience, which shows little or no evidence of sensitization in patients receiving MAL cream.

Even under these extreme conditions of exposure, MAL cream did not induce cross-sensitization towards ALA, which is an endogenous substance. No subject reported a positive reaction to ALA (see Table 27 above).

The prolonged use of MAL cream caused marked erythema, which resolved within a few days. This was concluded to be drug-related since MAL vehicle did not cause such reactions.

Also, the subjects that had a high irritation score (5 or 6) in the induction phase had a greater risk for sensitization in the challenge phase.

It is concluded that MAL cream has the potential to sensitize, but without cross-sensitization to ALA and that it can cause local irritation after long exposure as demonstrated by erythema. The results from this study also show that there is a close relationship between irritation and sensitization. Both the sensitization and the irritancy are related to the drug substance and not to the vehicle.

5.5.3.5 Interpretation

The clinical relevance of the findings in Study 110/03 is highly questionable since the exposure to MAL in the course of this study differed markedly from that in clinical practice in 3 major ways:

- There was continuous exposure to MAL for 3 weeks followed by a challenge 2 weeks later lasting 48 h. By contrast clinical exposure during treatment of AK and BCC skin lesions is restricted to 2 sessions of just 3 hours per session with an interval of one week between treatment sessions with the cycle repeated after three months if required for BCC.

- The treated areas were not illuminated at any time so that no photobleaching occurred whereas in clinical practice, the area is illuminated after each 3 h application. It has

been established that photobleaching using the standardized illumination parameters is complete so that no further exposure to drug residing in the skin is possible.

- Skin exposed to MAL cream was covered by an aluminum (Finn) chamber, which was fixed in place by adhesive Scanpore tape. In addition, opaque adhesive tape was applied to prevent exposure to light through the Scanpore tape. The Finn chamber and the opaque adhesive tape created a microenvironment in the exposed skin that most probably enhanced penetration of methyl aminolevulinate as compared to the clinical situation. This is quite different from the Tegaderm covering which is removed after the 3 h application in clinical practice.

- Thus, Study 110/03 addresses the potential of MAL to cause sensitization under extreme conditions but does not reflect the situation in clinical practice. The situation may be compared with that of benzoyl peroxide (BPO), an active ingredient in BenzaClin (NDA 50-756), which is marketed for "Topical treatment of acne vulgaris". Under maximized conditions BPO is reported to give a high rate of sensitization. In contrast, in studies using BPO under normal conditions of use, sensitization is a rare occurrence. There is an apparent discrepancy between the sensitization rates observed under maximized conditions compared to normal conditions of use. One possible explanation is difference in the amount of product penetrating through the stratum corneum in the 2 different conditions.

5.5.4 Overall Discussion and Conclusions

The results suggest that mild and moderate cumulative irritancy can be detected in the methyl aminolevulinate group when cream has been present on the skin for 4 or more days. No reactions were detected in the vehicle group; this suggests that the other ingredients in the cream do not irritate normal skin.

In conclusion, the results from the 21 days sensitization potential study show that MAL cream can induce sensitization in over half those exposed to these extreme conditions but that there is no cross-sensitization to the endogenous ALA. MAL cream has been on the market for close to 2 years and around 25,000 MAL-PDT treatments have been performed. Only one instance of sensitization towards MAL 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.

Lastly, health care professionals applying the cream will be protected by the 2 following barriers:

- Medical gloves; PhotoCure has tested and identified medical gloves that MAL cream does not penetrate; and

- It is recommended that cream application is done using a spatula.

6 PHASE III PROGRAM

The Phase III program was comprised of 6 studies as follows:

- Two double-blind, randomized, placebo-controlled trials in patients with low-risk risk nodular lesions (Studies 307/00 and 308/00, conducted in the United States and Australia, respectively);
- One open, randomized, controlled trial with simple surgical excision as comparator in patients with low-risk nodular lesions (Study 303/99, conducted in Europe);
- One open, randomized, controlled trial with cryotherapy as comparator in patients with low-risk superficial lesions (Study 304/99, conducted in Europe); and
- Two uncontrolled studies in high-risk patients with nodular and superficial BCC lesions unsuitable for conventional therapy (Studies 205/98 and 310/00, conducted in Europe and Australia, respectively).

This program was designed to demonstrate efficacy and safety for treatment with MAL-PDT in 2 distinct BCC populations, namely superficial and nodular low-risk and high-risk BCC.

6.1 Trial Design and Blinding

6.1.1 Studies 307/00 and 308/00

These 2 double-blind, randomized, placebo-controlled studies included patients with low-risk primary nodular BCC lesions.

The primary objective was to compare the patient complete response rate 6 months after the last PDT treatment cycle. Response was assessed by histological evaluation of the excised treatment sites (Figure 14).

Patients were randomized to receive MAL or placebo cream after informed consent was obtained. Both investigator and patient were blinded to the content of the cream (active or vehicle) and the 2 formulations had identical appearance and consistency to ensure blinding. Since patients receiving active treatment are expected to have a higher rate of local phototoxic reactions during illumination than the placebo group, all procedures related to administration of light was handled by a nurse or research coordinator, who was not involved in the lesion evaluation. Consequently, the investigator, patient, and the sponsor were blinded to the identity of the test medication.

All patients received 1 treatment cycle consisting of 2 PDT sessions, with a 1-week interval. Lesions that were not clinically reduced by at least 50% at 3 months after the first treatment cycle were excised, while those showing a partial response, defined as at least a 50% reduction of lesion area but not 100%, were treated with a second cycle of MAL-PDT. Lesions with complete response were followed for an additional 6 months. Lesions failing to show complete response 3 months after the second MAL-PDT cycle were excised while those considered clinically to have shown a complete response were

excised after another 3 months had elapsed ie, 6 months after the last treatment. The primary outcome assessment was based on histological examination of the excised tissue, which was performed in a blinded manner at a central laboratory. The number of tissue blocks and slides was dependent on the size of the specimen. The entire specimen was sliced into sections of thickness not greater than 3 mm (Figure 14).

A flow chart for the studies is provided in Figure 15.

The studies were considered adequate and well controlled for establishing the efficacy of MAL-PDT. The studies were designed according to guidance received from FDA. Recurrence could not be assessed in this study, because of the complete excision of the affected area, but the cure rate versus potential for recurrence could be assessed by the detection rate of residual tumor cells on histological examination.

Figure 14: Processing of Excised Specimen

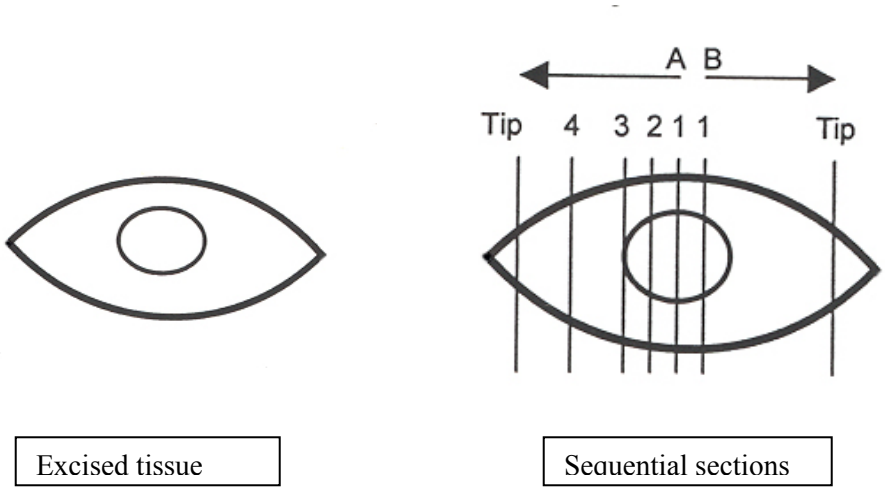
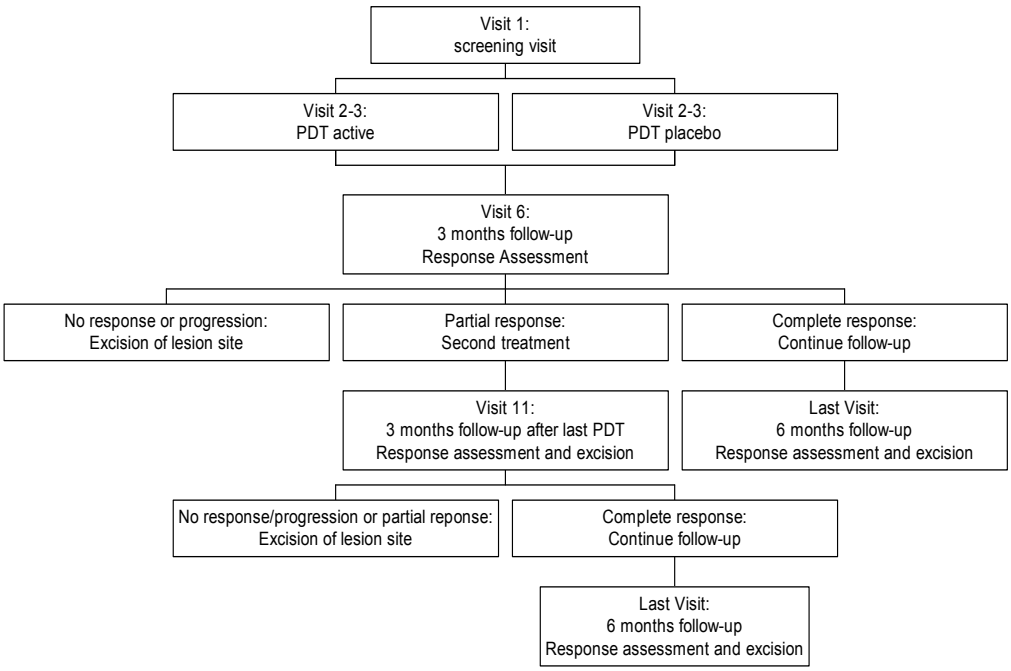


Figure 15: Flow Chart for Studies 307/00 and 308/00



6.1.2 Studies 303/99 and 304/99

These 2 randomized, active-controlled studies included patients with low-risk primary BCC lesions. The primary objective was to compare the patient complete response rate at 3 months after the last PDT or comparator treatment of the lesion area.

In Study 303/99, patients with primary nodular BCC lesions were randomized to 1 treatment cycle (2 PDT sessions 1 week apart) of MAL-PDT or simple excision surgery. Lesions with non-complete response in the MAL-PDT group at the 3-month follow-up visit were retreated with a second cycle of MAL-PDT and assessed again 3 months later.

In Study 304/99, patients with primary superficial BCC lesions were randomized to 1 PDT session (1 PDT only) or cryotherapy. Lesions with non-complete response at the 3-month follow-up visit were retreated with 1 treatment cycle of MAL-PDT (2 PDT sessions, also given 1 week apart). Cryotherapy was repeated if the response was non-complete. Response evaluation was performed clinically 3 months after the last PDT or cryotherapy.

Secondary objectives were to compare the safety, cosmetic outcome, and long-term (up to 5 years) recurrence rates of the treatment modalities. Twenty-four month follow-up data are currently available for these 2 studies. Long-term response was assessed clinically with histological confirmation by biopsy only if recurrence was suspected.

Both studies were non-blinded, since the procedures used for the different treatment modalities prevent blinding of the patient and the investigator. The question of whether an independent clinician could have made blinded assessments must be considered. At the time the studies were designed, the sponsor thoroughly evaluated whether this was feasible and consulted with expert dermatologists. It was concluded that it is not possible for an assessor to be truly blind to treatment. A surgical scar is very obvious and cryotherapy frequently leaves an area of depigmentation and sometimes an area of depression. Thus, nominally blinded assessments would in fact be pretence. Photography is an alternative approach, but this too has serious drawbacks. The conditions for photography such as lighting, distance of the camera from the lesion, focal length of the lens, exposure etc must be standardized. This is possible at a single site but very difficult, if not impossible to achieve in a multicenter study. Also, the clinician uses palpation as well as inspection and a residual lesion is often not visible but is palpable. Thus, clinical assessment is the more sensitive and hence more conservative in terms of response to treatment but cannot be blinded.

6.1.3 Studies 205/98 and 310/00

These 2 open studies included patients with high-risk superficial and nodular BCC lesions unsuitable for conventional therapy. A comparator was not employed, since by definition patients were unsuitable for treatment modalities such as radiotherapy or surgical excision followed by reconstructive surgery due to possible morbidity and poor

cosmetic outcome. For Study 205/98, an independent review board evaluated the patients included to verify adherence to the inclusion criteria.

In Study 205/98, lesions with no response to therapy at the 3-month visit were considered treatment failures and were not re-treated. Lesions showing partial response, defined as a 50% or greater reduction in lesion area, received a second treatment cycle of two sessions of PDT one week apart. In Study 310/00, all lesions showing a non-complete response (ie, partial or no response) at 3 months were eligible to receive a second treatment cycle of 2 sessions a week apart.

The primary objective was to describe the patient complete response rate at 3 months after the last PTD treatment cycle. The 3-month clinical tumor response assessment was confirmed by histology from biopsies taken in the treated lesion area. Twenty-four month follow-up data of patients enrolled in Study 205/98, and 12-month follow-up data of patients enrolled in Study 310/00 have been reported and recurrence rates are being evaluated in those patients for up to 5 years.

6.2 Trial Populations – Diagnosis and Grading of Lesions

The diagnosis of every BCC lesion was confirmed by histology in all Phase III studies. Tumors were classified by the dermatologist as superficial, nodular, or mixed. BCCs deemed unsuitable for conventional therapy were termed “high-risk”, also described as “difficult to treat”.

Separate trials were performed in patients with low-risk nodular (three trials) and superficial (one trial) BCC. This separation into different trials is entirely appropriate since it cannot be assumed that the different morphological types of BCC respond in a similar manner. Each of the controlled trials had adequate statistical power to make a clinically meaningful comparison of outcomes, which is far more robust than post-hoc subgroup analyses. The investigation of high-risk patients as a separate population (2 trials) is also fully justified since it is recognized that the behavior of these lesions, their prognosis and treatment options are distinct from low-risk lesions.

The definition of ‘high-risk’ used in each of the trials is based on that of Randle[16] and others[20,30], and is consistent with standard texts[3,13,43] However, pure morpheaform and/or highly infiltrated lesions assessed clinically and/or by histology were excluded. A mixed nodular/morpheaform lesion that was not highly infiltrated (clinically) may have been included.

The precise eligibility criteria in the 2 trials differed somewhat:

Study 205/98:

Recurrent lesion:	treatment failure after 2 previous treatments in 1 year; and/or
Large lesion:	greatest diameter >20 mm on extremities, >30 mm on trunk or >15 mm on face: and/or
Mid-face lesion:	nose, nasolabial, and orbital areas; and/or

Lesion: located in severe sun-damaged skin in which surgery or radiation therapy is not suitable due to frequent recurrences.

An independent Study Review Board (SRB) verified patient inclusion with respect to compliance with these criteria and lesions that were judged to be amenable to conventional methods of treatment were excluded from the efficacy data set.

Study 310/00:

In Study 310/00, the definition of high-risk was modified slightly as follows:

> A large BCC lesion with the largest diameter ≥ 15 mm on extremities, except below knees, where the largest diameter ≥ 10mm, ≥ 20 mm on the trunk or ≥ 15 mm on the face.
>
> A BCC lesion in mid-face region H-zone according to Swanson[30] (nose, nasolabial, periorbital, periauricular areas and temple) or on the ear.

The exclusion of 'recurrent' from the eligibility criteria implies that recurrence per se was insufficient to classify a lesion as 'high-risk'. Since recurrence is a risk factor for further recurrence, this is perhaps excessively conservative to exclude it. In practice, many of the lesions included on the basis of size or location were also recurrent; therefore the difference between Studies 205/98 and 310/00 in this respect is probably more theoretical than actual. The decision to exclude the eligibility criterion 'located in severely sun-damaged skin' from the second study is desirable since most BCC lesions occur in sun-damaged skin and a decision on whether the skin is suitable for surgery or radiotherapy is subjective and rather arbitrary.

By protocol amendment of Study 310/00, per request of the FDA and with consensus of participating dermatologists, the definition of 'high-risk' was broadened to include "patients at high risk of surgical complications" (patients with bleeding disorders, anticoagulant treatment, cardiac risk factors, or risk of poor surgical compliance). This decision can be criticized from the theoretical point of view that the majority of lesions in such patients will have a prognosis that is indistinguishable from low-risk lesions in other patients. However, the decision reflects the therapeutic need of practicing clinicians and their patients to employ a treatment which will be well tolerated by these patients who are not candidates for surgery due to high co-morbidity and potential for serious morbidity and mortality. Inclusion of this group is therefore appropriate.

In Studies 307/00, 308/00, 303/99, and 304/99, low-risk superficial and nodular BCC lesions were included, ie, those lesions that would not be defined as high-risk in Studies 205/99 and 310/00.

6.2.1 Treatment

6.2.1.1 Preparation of Lesions

Care was taken to train all investigators in the methodology of PDT, both through practical training sessions and by supplying videos to all sites. Lesions were prepared by

roughening the surface in order to facilitate access of cream and light to all parts of the lesion. For superficial BCCs, this was done by removal of crust with a small curette and scraping. For nodular BCCs, the normal epidermal keratin layer was removed. Further preparation was confined within the limits of the tumor without any attempt to excise beyond the tumor margins. Lesions were prepared before each treatment session.

In the placebo-controlled studies, (Studies 307/00 and 308/00), lesion preparation was done for all lesions, including placebo lesions.

6.2.1.2 Application of MAL (and Placebo) Cream

MAL cream was applied to lesions and a margin (5 to 10 mm) of surrounding skin in a 1-mm thick layer. The area was then covered with an adhesive occlusive dressing. After 3 hours the dressing was removed, excess cream was cleaned off gently with saline solution and illumination performed immediately. It is apparent that there was a high degree of compliance with these procedures in the clinical trials.

For the placebo-controlled trials (Studies 307/00 and 308/00) the vehicle cream was applied in the same manner as MAL cream.

6.2.1.3 Light Source and Illumination

All investigational centres made use of the Curelight lamp, which emits red light of wavelength 570-670 nm from a 150-Watt halogen lamp collimated by means of an elliptical mirror and focused by a lens through various filters. These filters remove infrared light (>670 nm), thereby avoiding heating. Blue light is also eliminated completely. Thus, red light, which penetrates tissues more deeply than blue light, was selected. The Curelight™ lamp gives a fluence rate at the skin surface of approximately 50-200 mW/cm^2 depending on the diameter of the light field, which can be varied from 30 to 55 mm in diameter. This is monitored by a detector placed on the skin after cream removal, prior to illumination. The fluence (total energy of light) is easily controlled and the total light dose delivered to the lesion is therefore precise. Total light dose was intended to be 75 J/cm² in all trials.

Overall, the design of the lamp and its utilization in the development program of MAL-PDT give confidence about the safety and reproducibility of illumination that was used in the clinical trial program and its applicability to routine clinical practice.

6.2.1.4 Excision Surgery

In Study 303/99, the width of the surgical margin was measured and recorded for each lesion in the excision surgery treatment group. Patients randomized to simple excision surgery were to be treated according to investigator routine but standardized conservatively, using 5-mm margins, regardless of lesion size.

6.2.1.5 Cryotherapy

In Study 304/99, cryotherapy was performed with a hand-held liquid nitrogen spray, using a double freeze-thaw cycle. After an initial ice field formation with a 3-mm rim of

clinically healthy tissue, the ice field was to be maintained for a minimum of 20 seconds. This procedure was repeated after a thaw of 2-3 times the freeze time.

6.2.2 Histological Response Assessment

In the placebo-controlled studies of nodular low-risk BCC (Studies 307/99 and 308/00), the whole treatment site was excised and examined histologically 6 months after the last PDT session. Lesion depth was only recorded in these studies since depth derived from biopsies may be misleading.

In the 2 ongoing, 5-year follow-up, active-controlled trials (Studies 303/99 and 304/99) histological verification of response by punch biopsy was only performed in case of suspected non-complete response or recurrence.

In the non-controlled trial of 'high-risk' BCC in Europe (Study 205/98), the clinical response assessment was verified by a single punch biopsy. In the Australian 'high-risk' study (Study 310/00) the response assessment was verified by multiple punch biopsies, using a grid with 1-cm^2 squares.

6.2.3 Primary and Secondary Endpoints

The patient complete response rate is the primary endpoint in all of the Phase III studies. For patients with one lesion, this is of course equal to the lesion response rate. For patients with more than one lesion, the patient complete response rate will inevitably be lower than the lesion response rate. The more lesions within an individual patient the greater the difference will be, and a weighting factor has therefore been applied to give a mean weighted patient response rate. This was a secondary endpoint and is similar to but not identical to the lesion response rate, which also comprised a secondary endpoint in each of these studies. The patient complete response rate is the most conservative of these endpoints and it is therefore an appropriate primary endpoint. However, it could be argued that lesion response is a more rational choice of primary outcome since the size, location and histological type of lesion are important determinants of the response to treatment. Nevertheless, the studies comply with FDA's request to use patient response. In practice, the difference between the endpoints is not likely to make a large difference to the overall results in BCC in which a majority of patients have a single lesion, particularly those with nodular lesions.

The patient response is based on the lesion responses defined according to modified World Health Organization (WHO) criteria for tumor response as 'Complete Response (CR)' (complete disappearance of lesion), Partial Response' (50% or greater decrease in total lesion area) and 'No Response'. The assessments were made 3 months after the last treatment in all studies except Study 307/00 when the final excision was performed after a further 3 months had elapsed. Up to three months are required for regeneration of normal skin and complete loss of crusts and erythema resulting from the MAL-PDT treatment. It is therefore an appropriate time for assessment of response including cosmetic outcome. Recurrence was defined as reappearance of a previously treated and eradicated lesion.

In addition to response rate, excellent cosmetic outcome is of crucial importance to the BCC patient and this should be a major objective in BCC treatment. Cosmetic outcome also reflects the degree of tissue preservation, and is therefore an important secondary efficacy parameter. Care was taken to score the various components of this, namely scarring, atrophy, induration, redness and change in pigmentation on a subjective but simple and therefore reliable scale of excellent, good, fair or poor. In addition to this global assessment, the outcome of each individual lesion site was graded with regard to presence of hypo-, hyperpigmentation, scarring and tissue defects (none, slight, obvious).

From Phase III, the cosmetic outcome was 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.

Five-year recurrence rates will be determined in all studies, except Study 307/00 and Study 308/00, where the lesion sites are excised, and long-term follow-up would therefore be meaningless. Recurrence rates are reported annually in separate follow-up reports for each study.

6.2.4 Safety Parameters

Adverse events (AEs) in the Phase III studies were reported either spontaneously by the patient or elicited through open (non-leading) questioning during and at the end of the study. As far as possible, AEs were described by duration, severity, relation to treatment and by the need for specific therapy. Severity was rated as mild, moderate or severe and the term 'treatment-related' is defined as those AEs to which the relation to treatment was coded: 'YES', or 'UNCERTAIN'. Local skin reactions including expected local phototoxic reactions were recorded as AEs. Other AEs including serious adverse events (SAEs) were handled in a conventional manner according to ICH guidelines. AEs were coded according to WHO criteria and terminology with additional codes created to describe adequately the local phototoxic AEs.

A description of overall safety evaluation for all studies and the safety results are provided in Section 8.

6.2.5 Populations for Statistical Analysis

For the placebo-controlled studies 307/00 and 308/00 the primary efficacy analysis as well as the safety evaluations were performed on the population of patients who received at least one study treatment ie, Intention to Treat (ITT). Additional analyses were also performed on the Per Protocol (PP) populations. In practice the small number of dropouts

had no effect on the results. For the active comparator studies 303/99 and 304/99 the primary efficacy analysis was based on the PP populations since this is the more conservative approach ie, it is less likely to lead to the conclusion that the test treatment is no different from the reference. The choice of statistical methods depended on the distribution of the data and the purpose of the study. For all studies, data are presented using summary statistics and 95% CIs as appropriate. Safety data are summarized and listed.

6.2.6 Statistical Analyses

6.2.6.1 Patient Complete Response

The patient CR rate was summarized within each treatment using counts and percentages of patients. The 95% confidence interval (CI) was calculated for each treatment. In the two placebo-controlled studies, the patient CR rate was analyzed using the Cochran-Mantel-Haenszel (CMH) test with a significance level of 5% because it allows an adjustment for center effects. This was performed using PROC FREQ in SAS and the CMH where the results of type 2 (row mean scores differ) are of interest. The Breslow-Day test for homogeneity of the odds ratios across centers was also performed to evaluate center by treatment interactions.

In Studies 303/99 and 304/99, MAL-PDT was to be considered acceptable if it was demonstrated that the patient complete response rate was no more than 15% inferior to the active comparator (surgery or cryotherapy respectively). The 15% level was pre-defined in consultation with the investigators as clinically relevant. The one-sided upper 97.5% confidence limit for the difference in patient CR rates between surgery or cryotherapy and MAL-PDT was calculated. This upper limit was required to be below 15% to conclude that MAL-PDT is non-inferior to the comparator. This test was based on the PP population for both studies. The one-sided upper 97.5% confidence limit for the difference in CR rates between MAL-PDT and the comparator was calculated using Mantel-Haenszel weights to account for center effects.

For Studies 205/98 and 310/00, 2-sided 95% confidence intervals for patient CR rates in the studies of BCC unsuitable for conventional therapy were calculated.

In Study 205/98, the primary efficacy variable was patient response and the following hypothesis tested using an exact test for a binomial proportion:

H0: Fair/excellent/complete response rate of MAL-PDT ≤50%

versus the alternative hypothesis:

HA: Fair/excellent/complete response rate of MAL-PDT >50%.

In Study 310/00, the following hypothesis tested using an exact test for a binomial proportion:

H0: Complete response rate of MAL-PDT ≤65%

versus the alternative hypothesis:

HA: Complete response rate of MAL-PDT >65%.

6.2.6.2 Other Responses (Lesion Response, Cosmetic Outcome and Recurrence Rate)

The lesion complete response rate was summarized using counts and percentages of lesions.

Overall cosmetic outcomes, as evaluated by the investigator and patient, were summarized within each treatment using counts and percentages of patients. The 95% CI for the percentage of patients having an excellent cosmetic outcome was calculated for each treatment.

Missing lesion assessments were not substituted but presented as missing in the tables for the ITT population, and excluded for the PP population. However, in the 2 placebo-controlled studies (Studies 307/00 and 308/00), missing data on lesion assessments were categorized as non-complete response.

Patient recurrence rates at 12 and 24 months were based on the lesion recurrence assessment. A patient was regarded as non-recurrent if none of their lesions was recurrent. If a patient had any lesions with missing recurrence assessment, patient recurrence was regarded as missing. The denominator in the PP population thus decreased over time. For the ITT population, the missing values were displayed as missing in the tables. The difference between the comparator and MAL-PDT treatments in patient recurrence rate was estimated along with 2-sided 95% confidence intervals.

7 EVALUATION OF EFFICACY

7.1 Overall Patient Population

The total population comprising the 6 pivotal Phase III studies was 484 patients with BCC of whom 480 (99%) were treated and included in the ITT and safety populations (Table 28). Of these 480 patients, 341 (71%) were treated with MAL-PDT and the remainder with placebo, surgery, or cryotherapy as comparators. The ITT population comprised 697 lesions of which 498 (71%) were treated with MAL-PDT. The PP population comprised 451 patients of whom 317 (70%) were treated with MAL-PDT and the remainder with comparators. The PP population comprised 632 lesions of which 448 (71%) were treated with MAL-PDT.

The demographic distribution of the study population with respect to age, gender and race, reflects that of the patient population affected by BCC: mean age 66 ± 14 years; 63% male; all Caucasian. Study 307/00 was conducted in the United States, Studies

308/00 and 310/00 were conducted in Australia, and Studies 205/98, 303/99, and 304/99 in Europe.

Table 28: Clinical Trial Population

Study	Treatment	Number of Patients N (%)	Safety and ITT Analysis n (%)	PP Analysis n (%)
Low-Risk Nodular				
307/00	MAL-PDT	33 (51%)	33 (100%)	31 (94%)
	Placebo-PDT	32 (49%)	32 (100%)	32 (100%)
	Total	65 (100%)	65 (100%)	63 (97%)
308/00	MAL-PDT	33 (50%)	33 (100%)	33 (100%)
	Placebo-PDT	33 (50%)	33 (100%)	33 (100%)
	Total	66 (100%)	66 (100%)	66 (100%)
303/99	MAL-PDT	53 (51%)	52 (98%)	50 (94%)
	Surgery	50 (49%)	49 (98%)	47 (94%)
	Total	103 (100%)	101 (98%)	97 (94%)
All nodular		**234**	**234 (100%)**	**226 (97%)**
Low-Risk Superficial				
304/99	MAL-PDT	62 (52%)	60 (97%)	58 (94%)
	Cryotherapy	58 (48%)	58 (100%)	57 (98%)
	Total	120 (100%)	118 (98%)	115 (96%)
All superficial		**120**	**118 (98%)**	**115 (96%)**
High-Risk				
205/98	MAL-PDT	94	94 (100%)	85 (90%)
310/00	MAL-PDT	102	102 (100%)	95 (93%)
All High-Risk		**196**	**196 (100%)**	**180 (92%)**

The Phase III clinical trial program in BCC was aimed at 2 different groups of patients:

1. Patients with primary superficial and nodular low-risk BCC (suitable for conventional therapy); and
2. Patients with primary or recurrent superficial and/or nodular high-risk BCC (unsuitable for conventional therapy).

In support of the treatment of nodular and superficial low-risk BCC and in consultation with FDA (End of Phase II meeting, 22 June 2000) 2 randomized, double blind, placebo-controlled multicenter studies were performed under IND No. 59.221. In these studies (307/00 and 308/00), the efficacy response was assessed by complete excision of the treated area and histological examination 6 months after treatment. One of these studies was performed in the United States and the other in Australia. A third study (Study 303/99), performed in Europe, used excision surgery, the most widely accepted treatment of nodular BCC, as an active comparator and results were assessed clinically. A fourth study (Study 304/99), performed in Europe in superficial BCC, used cryotherapy as an active comparator. Assessment of recurrence rates is ongoing; results at 24 months are presented and patients with complete clinical response will be followed for 5 years.

Two open studies without comparators were performed in support of the treatment of high-risk BCC (Studies 205/98 and 310/00). Both nodular and superficial high-risk BCC lesions were eligible for inclusion into these studies.

7.2 Efficacy in Low-Risk Primary, Superficial, and Nodular BCC

7.2.1 Efficacy in Low-Risk Primary Nodular BCC

7.2.1.1 Patient and Lesion Disposition

7.2.1.1.1 Patient Disposition

Table 29 summarizes the numbers of patients randomized and treated in the 2 placebo-controlled studies (Studies 307/00 and 308/00) and the surgery-controlled study (Study 303/99) of nodular BCC. All randomized patients in the placebo-controlled studies were treated and all but 2 in the active comparator study.

Table 29: Patients Randomized and Treated

Studies of Primary Nodular BCC

Study	MAL-PDT* N (%)	Placebo-PDT* N (%)	Surgery N (%)	Total N (%)
307/00				
Randomized	33 (51%)	32 (49%)		65 (100%)
Treated	33 (100%)	32 (100%)		65 (100%)
308/00				
Randomized	33 (50%)	33 (50%)		66 (100%)
Treated	33 (100%)	33 (100%)		66 (100%)
303/99				
Randomized	53 (51%)		50 (49%)	103 (100%)
Treated	52 (98%)		49 (98%)	101 (98%)
Total				
Randomized	119 (51%)	65 (28%)	50 (21%)	234 (100%)
Treated	118 (99%)	65 (100%)	49 (98%)	232 (99%)

* Two sessions of MAL-PDT or placebo-PDT in Studies 307/00, 308/00, and 303/99. After 3 months, lesions with PR (307/00 and 308/00) or non-CR (303/99) received 2 additional sessions of PDT treatment.

Data Source: Statistical Table 1.1 in Section 12, BCC ISE.

7.2.1.1.2 Lesion Disposition

Table 30 summarizes the lesion disposition data. In each study, over 90% of all the randomized lesions were treated. The reason for not treating randomized lesions was either because the clinical diagnosis of BCC was not confirmed by biopsy or because the patient withdrew consent.

Table 30: Number of Lesions Randomized and Treated

Studies of Nodular BCC

Study	MAL-PDT* N (%)	Placebo-PDT* N (%)	Surgery N (%)	Total N (%)
307/00				
Randomized	45 (52%)	41 (48%)		86 (100%)
Treated	41 (91%)	39 (95%)		80 (93%)
308/00				
Randomized	36 (49%)	38 (51%)		74 (100%)
Treated	34 (94%)	36 (95%)		70 (95%)
303/99				
Randomized	60 (51%)		58 (49%)	118 (100%)
Treated	55 (92%)		55 (95%)	110 (93%)
Total				
Randomized	141 (51%)	79 (28%)	58 (21%)	278 (100%)
Treated	130 (92%)	75 (95%)	55 (95%)	260 (94%)

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR (307/00 and 308/00) or non-CR (303/99) received 2 additional sessions of PDT treatment.
Data Source: Statistical Table 1.2 in Section 12, BCC ISE.

7.2.1.2 Patient Demography and Baseline Lesion Characteristics

Table 31 summarizes the demography of the ITT populations in each of the studies. All treated patients were Caucasian. The mean age of around 67 years and predominance of males is typical of BCC patient populations worldwide. The treatment groups in all studies were well matched for age distributions and were similar across studies.

Table 31: Patient Demography

Studies of Nodular BCC (ITT)

Study Variable	MAL-PDT	Placebo-PDT	Surgery	Total	P-Value *
307/00	N=33	N=32		N=65	
Age (years)					0.5962
Mean ±SD	62 ±14	67 ±14		65 ±14	
Median	62	71		65	
Min – Max	28 – 88	39 – 88		28 – 88	
Sex (N, %)					0.7234
Male	25 (76%)	25 (78%)		50 (77%)	
Female	8 (24%)	7 (22%)		15 (23%)	
308/00	N=33	N=33		N=66	
Age (years)					0.4360
Mean ±SD	70 ±10	66 ±11		68 ±11	
Median	70	68		68	
Min – Max	48 – 87	40 – 88		40 – 88	
Sex (N, %)					0.1621
Male	22 (67%)	27 (82%)		49 (74%)	
Female	11 (33%)	6 (18%)		17 (26%)	
303/99	N=52		N=49	N=101	
Age (years)					0.6658
Mean ±SD	69 ±11		67 ±11	68 ±11	
Median	70		69	70	
Min – Max	40 – 95		38 - 82	38 – 95	
Sex (N, %)					0.8325
Male	32 (62%)		29 (59%)	61 (60%)	
Female	20 (38%)		20 (41%)	40 (40%)	

* P-Values for difference in sex distribution between treatment groups is from the CMH test adjusted for centre. P-Values for difference between treatment groups in age are from the ANOVA with factors treatment, center and their interaction.
Data Source: Statistical Tables 1.5, 1.9 and 1.10 in Section 12, BCC ISE.

7.2.1.2.1 Number of Lesions

As expected for nodular BCC, the large majority of patients had only 1 lesion and most of the remainder had two. Within each study, the number of lesions per patient was generally comparable between the treatment groups. In Study 303/99 there were 12% (6/55) with 2 lesions in the surgery group compared with 6% (3/55) in the MAL-PDT group, but the numbers are small and the difference is not statistically significant.

7.2.1.2.2 Location of Lesions

Table 32 shows the location of lesions in each of the studies. It should be noted that nodular lesions in the mid-face region including periorbital area, ears or nasolabial fold, were excluded from all of these studies. Lesions on the extremities were less frequent than at other sites in each of the studies but there was some variation in the proportion of lesions at each location between studies and between treatment groups within each study.

Table 32: Location of Lesions

Studies of Nodular BCC (ITT)

Study Location	MAL-PDT N (%)	Placebo-PDT N (%)	Surgery N (%)	Total N (%)
307/00	N=41 lesions	N=39 lesions		N=80 lesions
Face/Scalp	10 (24%)	15 (38%)		25 (31%)
Neck/Trunk	27 (66%)	15 (38%)		42 (53%)
Extremities	4 (10%)	9 (23%)		13 (16%)
308/00	N=34 lesions	N=36 lesions		N=70 lesions
Face/Scalp	9 (26%)	8 (22%)		17 (24%)
Neck/Trunk	14 (41%)	20 (56%)		34 (49%)
Extremities	11 (32%)	8 (22%)		19 (27%)
303/99	N=55 lesions		N=55 lesions †	N=110 lesions
Face/Scalp	22 (40%)		32 (58%)	54 (49%)
Neck/Trunk	27 (49%)		16 (29%)	43 (39%)
Extremities	6 (11%)		5 (9%)	11 (10%)

† Location not recorded for 2 lesions
Data Source: Statistical Table 1.17 in Section 12

7.2.1.2.3 Lesion Size

Table 33 shows the mean ± SD largest lesion diameter BCC for each patient prior to treatment. The range of largest diameters is very similar for all the studies and treatment groups. The mean largest lesion diameters were slightly greater in the active comparator study than in the placebo-controlled study but the differences are small and, more importantly, the size of lesions was well matched between treatment groups within each study. Largest lesion diameter was stratified in later statistical analyses into the following three groups: up to 10 mm, >10-20 mm and >20 mm.

Table 33: Mean Largest Lesion Diameter (mm) per Patient Before Treatment

Studies of Nodular BCC (ITT)

Study Characteristic	MAL-PDT	Placebo-PDT	Surgery	Total	P-Value *
307/00	N=33	N=32		N=65	0.9942
Mean ± SD	8.9 ± 3.1	9.4 ± 3.8		9.1 ± 3.5	
Median	8.0	8.5		8.0	
Min – Max	6.0 - 20.0	6.0 - 20.0		6.0 - 20.0	
308/00	N=33	N=33		N=66	0.9913
Mean ± SD	8.5 ± 3.0	8.6 ± 3.3		8.6 ± 3.2	
Median	8.0	8.0		8.0	
Min – Max	6.0 - 20.0	6.0 - 22.0		6.0 - 22.0	
303/99	N=52		N=49	N=101	
Mean ± SD	11.0 ± 3.8		10.9 ±4.4	11.0 ± 4.1	0.8006
Median	10.0		9.0	10.0	
Min – Max	6.0 - 20.0		6.0 - 26.0	6.0 - 26.0	

*P-Values for difference between treatment groups in largest lesion diameter per patient are from the ANOVA with factors treatment, center and their interaction.
Data Source: Statistical Tables 1.15 and 1.23 in Section 12, BCC ISE.

7.2.1.2.4 Lesion Depth

The depth of each lesion before treatment was measured from the punch biopsy in placebo-controlled Studies 307/00 and 308/00. Table 34 shows that the mean lesion depth was similar in the 2 studies and the treatment groups within each study.

Table 34: Lesion Depth (mm) Pre-Treatment

Studies of Nodular BCC (ITT)

Study Characteristic	MAL-PDT	Placebo-PDT	Total	P-Value
307/00	N=33	N=32	N=65	0.9131
Mean ± SD	1.3 ± 0.9	1.3 ± 0.6	1.3 ± 0.8	
Median	1.0	1.4	1.1	
Min – Max	0.3 - 4.5	0.5 - 3.0	0.3 - 4.5	
308/00	N=33	N=33	N=66	0.6282
Mean ± SD	1.2 ± 0.6	1.1 ± 0.6	1.2 ± 0.6	
Median	1.2	1.0	1.1	
Min – Max	0.4 - 2.9	0.5 - 2.8	0.4 - 2.9	

*P-Values for difference between treatment groups in lesion depth are from the ANOVA with factors treatment, center and their interaction.
Data Source: Statistical Tables 1.19 and 1.25 in Section 12, BCC ISE.

7.2.1.3 Number of Treatment Sessions

As shown in Table 35, a majority of the patients in each treatment group had 1 PDT treatment cycle (ie, 2 treatment sessions one week apart). A greater proportion of patients (28%) in Study 307/00 had a second treatment cycle compared with those in Study 308/00 (14%) but the groups were well matched within study.

Table 35: Number of PDT Sessions per Patient

Studies of Nodular BCC (ITT)

Study Number of Sessions	MAL-PDT* N (%)	Placebo-PDT* N (%)
307/00	N=33	N=32
1	1 (3%)	0 (0%)
2	22 (67%)	24 (75%)
3		
4	10 (30%)	8 (25%)
308/00	N=33	N=33
1	1 (3%)	0 (0%)
2	27 (82%)	29 (88%)
3		
4	5 (15%)	4 (12%)
303/99	N=52	
1	3 (6%)	
2	37 (71%)	
3	2 (4%)	
4	10 (19%)	

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR (Studies 307/00 and 308/00) or non-CR (Study 303/99) received 2 additional sessions of PDT treatment. (The 303/99 protocol did not allow for repeated surgical excision.)

Data Source: Statistical Table 1.29 in Section 12, BCC ISE.

7.2.1.4 Surgical Margin Size (Study 303/99)

Mean surgery margins obtained in Study 303/99 is provided in Table 36. Overall, a conservative margin was used, on average ranging from 4.3 to 5.0 mm over all lesions.

Table 36: Mean Excision Surgery Margin

Study 303/99 (ITT)

Study Lesion size (mm)	Excision Surgery Margin (mm)
303/99	
0.1-10	N= 34
Mean ± SD	4.3 ± 1.1
Median	5.0
Min – Max	1 – 5
>10-20	N= 17
Mean ± SD	4.6 ± 0.9
Median	5.0
Min – Max	2 – 5
> 20	N= 2
Mean ± SD	5.0 ± 0.0
Median	5.0
Min – Max	5 - 5

Data Source: Statistical Table 1.39 in Section 12, BCC ISE.

7.2.1.5 Response in Placebo-Controlled Studies (Studies 307/00 and 308/00)

All complete response rates in the placebo-controlled studies refer to histological responses assessed by examination of the completely excised tissue from the treated area 6 months after the last PDT. Patients were considered to have a complete response if all of their lesions showed complete response.

7.2.1.5.1 Patient Response Rate

Table 37 shows the complete response rates for the ITT and PP populations for Studies 307/00 and 308/00. Based on the ITT populations, the patient complete response rates for MAL-PDT were 76% and 67% for Studies 307/00 and 308/00 respectively. The corresponding patient response rates to placebo-PDT response rates were 34% and 18% respectively. In both studies, MAL-PDT was clearly superior to placebo-PDT as shown by the 95% CIs of the response rates and the differences in rates between MAL-PDT and placebo-PDT. Using the Cochran-Mantel-Haenszel test for superiority adjusted for center effects, the superior efficacy of MAL-PDT over placebo is demonstrated with P=0.0011 in Study 307/00 and P=0.0002 in Study 308/00. There was no statistical significant difference between centers. The placebo response of 34% is slightly higher than expected. However, this can be partly explained by the treatment effect of the debulking procedures as part of the lesion preparations.[44] Nevertheless, there is no doubt about the efficacy of MAL-PDT.

Table 37: Patient Complete Response Rates

Placebo-Controlled Studies of Nodular BCC (ITT and PP)

Population	Study	MAL-PDT* n/N (%)	Placebo-PDT* n/N (%)	Estimated Difference for MAL-PDT minus placebo-PDT	P-Value †
ITT	**307/00**	25/33 (76%)	11/32 (34%)	41.77%	0.0011
		95% CI: 58%-89%	95% CI: 19%-53%	95% CI: 18%-65%	
PP	**307/00**	24/31 (77%)	11/32 (34%)	44.55%	0.0007
		95% CI: 59%-90%	95% CI: 19%-53%	21%-69%	
ITT	**308/00**	22/33 (67%)	6/33 (18%)	48.03%	0.0002
		95% CI: 48%-82%	95% CI: 7%-36%	95% CI: 24%-72%	
PP	**308/00**	21/29 (72%)	6/32 (19%)	54.56%	0.0001
		95% CI: 53%-87%	95% CI: 7%-36%	95% CI: 30%-79%	

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR received 2 additional sessions of PDT treatment.

† P-Values are from CMH (treatment effect)

Data Source: Statistical Tables 1.53, 1.54, 1.59, 1.60, 1.61, 1.63 and 1.65 in Section 12

7.2.1.5.2 Lesion Response Rate

Table 38 shows Lesion Complete Response rates with histological verification of response for the ITT and PP populations in Studies 307/00 and 308/00. Based on the ITT populations, the histological lesion complete response rates for MAL-PDT were 78% and 68% for Studies 307/00 and 308/00, respectively. The corresponding rates for

placebo-PDT were 33% and 19% respectively. In both studies, MAL-PDT was clearly superior to placebo-PDT.

Table 38: Lesion Complete Response Rates

Placebo-Controlled Studies of Nodular BCC (ITT and PP)

Study Population	MAL-PDT* n/N (%)	Placebo-PDT* n/N (%)
307/00		
ITT	32/41 (78%)	13/39 (33%)
PP	31/39 (79%)	13/37 (35%)
308/00		
ITT	23/34 (68%)	7/36 (19%)
PP	22/30 (73%)	7/33 (21%)

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR received 2 additional sessions of PDT treatment.
Data Source: Statistical Tables 1.43 and 1.44 in Section 12, BCC ISE.

7.2.1.5.3 Lesion Response by Location

Lesion CR rates in the ITT and PP populations stratified by lesion location are shown in Table 39. There were no clear differences in response rates dependent on location.

Table 39: Lesion Complete Response Rates by Lesion Location

Placebo-Controlled Studies of Nodular BCC (ITT and PP)

Study Lesion location	MAL-PDT* n/N (%)		Placebo-PDT* n/N (%)	
	ITT	**PP**	**ITT**	**PP**
307/00				
Face/Scalp	8/10 (80%)	7/9 (78%)	4/15 (27%)	4/14 (29%)
Trunk/Neck	20/27 (74%)	20/26 (77%)	6/15 (40%)	6/15 (40%)
Extremity	4/4 (100%)	4/4 (100%)	3/9 (33%)	3/8 (38%)
308/00				
Face/Scalp	8/9 (89%)	8/8 (100%)	1/8 (13%)	1/8 (13%)
Trunk/Neck	9/14 (64%)	8/12 (67%)	4/20 (20%)	4/18 (22%)
Extremity	6/11 (55%)	6/10 (60%)	2/8 (25%)	2/7 (29%)

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR received 2 additional sessions of PDT treatment.
Data Source: Statistical Tables 1.43 and 1.44 in Section 12

7.2.1.5.4 Lesion Response by Depth

Lesion Complete Response rates stratified by the depth of the lesions before treatment are shown in Table 40. The total number of lesions in subgroups is small; therefore, caution should be expressed in drawing conclusions. However, there is no clear relationship between lesion depth and response rate to MAL-PDT, and it would appear that the treatment is as effective for lesions of depth up to 5 mm as it is for thinner lesions. As expected, there is evidence that placebo treatment is less effective for deeper lesions ie,

the biopsy and preparation of lesions is effective for a proportion of thinner lesions though even for these it is clearly much less effective than MAL-PDT.

Table 40: Lesion Complete Response Rates by Lesion Depth at Baseline

Placebo-Controlled Studies of Primary Nodular BCC (ITT and PP)

Study Lesion Depth (mm)	MAL-PDT* n/N (%)		Placebo-PDT* n/N (%)	
	ITT	PP	ITT	PP
307/00				
<0.7	8/9 (89%)	7/8 (88%)	3/7 (43%)	3/5 (60%)
0.7 - 1.0	10/13 (77%)	10/12 (83%)	4/10 (40%)	4/10 (40%)
1.1-2.0	7/11 (64%)	7/11 (64%)	5/18 (28%)	5/18 (28%)
2.1 – 5.0	7/8 (88%)	7/8 (88%)	1/4 (25%)	1/4 (25%)
Total	32/41 (78%)	31/39 (79%)	13/39 (33%)	13/37 (35%)
308/00				
Missing	2/2 (100%)	2/2 (100%)	0/1 (0%)	0/1 (0%)
<0.7	6/7 (86%)	5/6 (83%)	2/9 (22%)	2/8 (25%)
0.7 - 1.0	4/5 (80%)	4/4 (100%)	3/11 (27%)	3/10 (30%)
1.1-2.0	10/18 (56%)	10/16 (63%)	2/12 (17%)	2/12 (17%)
2.1 – 5.0	1/2 (50%)	1/2 (50%)	0/3 (0%)	0/2 (0%)
Total	23/34 (68%)	22/30 (73%)	7/36 (19%)	7/33 (21%)

* Two sessions of MAL-PDT or placebo-PDT. After 3 months, lesions with PR received 2 additional sessions of PDT treatment.

Data Source: Statistical Tables 1.47 and 1.48 in Section 12, BCC ISE.

As shown in Figure 16 and Figure 17, MAL-PDT complete lesion response seems to be independent of lesion size and depth within the lesion population. However, the efficacy of placebo-PDT appears to depend on both lesion size and depth.

Figure 16: MAL-PDT

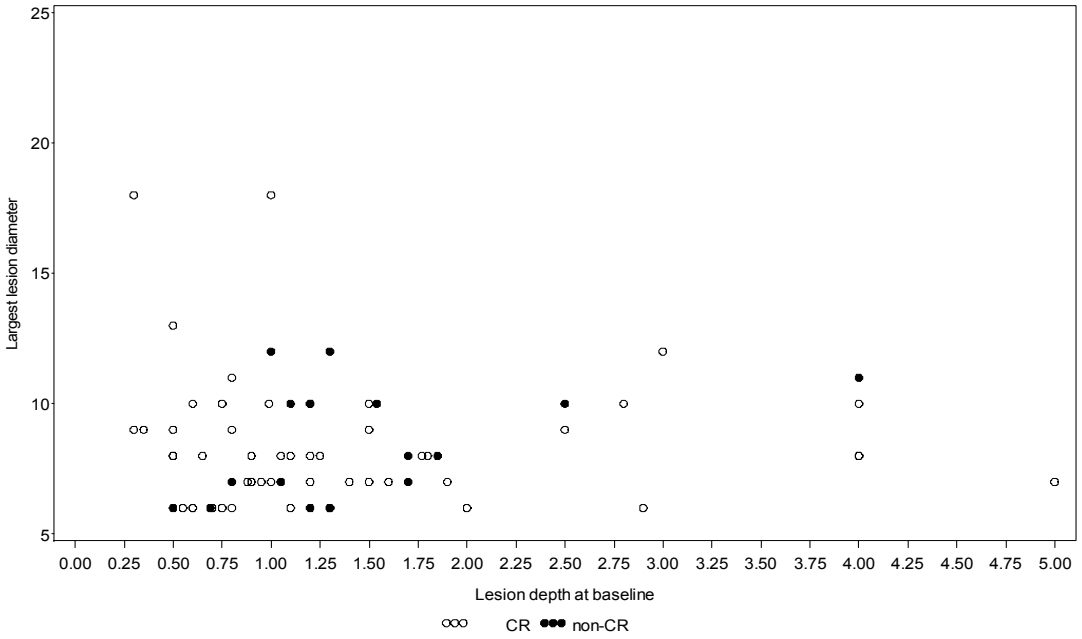
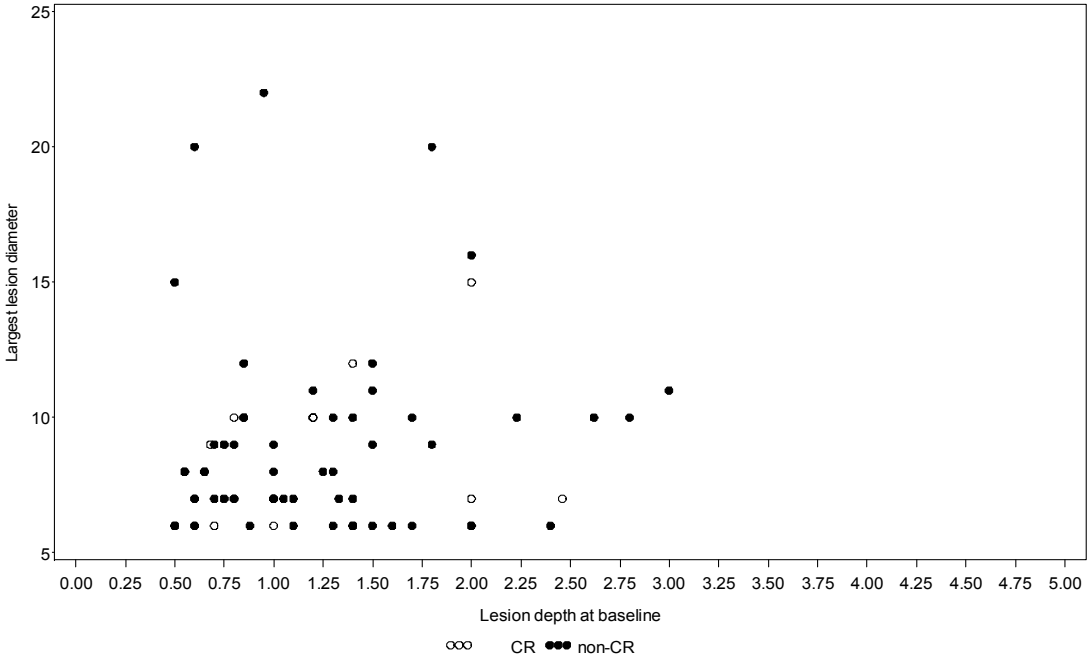


Figure 17: Placebo-PDT



7.2.1.5.5 Lesion Response by Number of Treatments

Lesion CR rates stratified by the number of treatment cycles received by each lesion are shown in Table 41. Very few lesions received either 1 or 3 treatment sessions; therefore, data were grouped as either 1 cycle (1 or 2 treatments) or 2 cycles (3 or 4 treatments). The superiority of active treatment over placebo is still apparent in patients requiring a second treatment cycle and the data demonstrate that the overall response rate can be increased by administering a second treatment at 3 months when the clinical evaluation shows a partial response at 3 months.

Table 41: Lesion Complete Response Rates by Number of PDT Cycles

Placebo-Controlled Studies of BCC (ITT and PP)

Study No of Cycles	MAL-PDT* n/N (%)		Placebo-PDT* n/N (%)	
	ITT	PP	ITT	PP
307/00				
1	23/28 (82%)	22/26 (85%)	9/30 (30%)	9/29 (31%)
2	9/13 (69%)	9/13 (69%)	4/9 (44%)	4/8 (50%)
308/00				
1	18/29 (62%)	18/26 (69%)	5/32 (16%)	5/29 (17%)
2	5/5 (100%)	4/4 (100%)	2/4 (50%)	2/4 (50%)

* Two sessions (1 cycle) of MAL-PDT or placebo-PDT. After 3 months, lesions with PR received 1 additional cycle of PDT treatment.
Data Source: Statistical Tables 1.49 and 1.50 in Section 12, BCC ISE.

7.2.1.5.6 Cosmetic Outcome

Cosmetic outcome was assessed of lesion areas in complete response 6 months after PDT. In the ITT population, the MAL-PDT group of the 2 studies, the investigator rated cosmetic outcome excellent in 59% to 61% of the lesions or excellent/good in 93% to 95% of the lesions. The results were slightly higher reported by the patients. The numbers for the placebo group are small and are not justified to be reported.

7.2.1.6 Response in Active-Controlled Study (Study 303/99)

7.2.1.6.1 Patient Response Rate

In Study 303/99, the lesion and hence patient complete responses were based on clinical assessment by the investigator. As in the placebo-controlled studies, patients were considered to have a complete response if 100% of their lesions showed CR 3 months after their last PDT or surgery. Table 42 shows Patient Clinical Complete Response rates for the ITT and PP populations treated with MAL-PDT or excision surgery.

Since the study was intended to show non-inferiority of MAL-PDT compared to surgery, the primary analysis was based on the PP population. MAL-PDT was to be considered non-inferior to simple surgical excision if it were demonstrated that the one-sided upper 97.5% confidence limit for the difference in CR rates was less than 15%. The patient CR rate with MAL-PDT was 90% and that with excision surgery was 98%. The

Mantel-Haenszel weighted treatment difference was 5.1% with upper 97.5% CI of 13.8%, supporting the hypothesis that MAL-PDT is non-inferior to surgery.

Table 42: Patient Complete Response

Active-Controlled Study of Nodular BCC (ITT and PP)

Study Population	MAL-PDT* n/N (%)	Excision Surgery n/N (%)	CMH-Estimated difference for surgery minus MAL-PDT
303/99			
PP	45/50 (90%) 95% CI: 78%-97%	46/47 (98%) 95% CI: 89%-100%	5.09% Upper 97.5% CI: 13.84%
ITT	45/52 (87%) 95% CI: 74%-94%	46/49 (94%) 95% CI: 83%-99%	NA

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.

Data Source: Statistical Tables 1.59, 1.60 and 1.66 in Section 12

7.2.1.6.2 Lesion Response Rate

Table 43 shows Lesion Clinical CR rates for the ITT and PP populations in Study 303/99. The primary analysis for the Patient Responses was based on the PP population. As expected, Lesion CR rates were very similar to the Patient CR rates with a 7% difference in favor of excision surgery.

Table 43: Lesion Complete Response Rates

Active-Controlled Study of Nodular BCC (ITT and PP)

Study Population	MAL-PDT* n/N (%)	Excision Surgery n/N (%)
303/99		
ITT	48/55 (87%)	51/55 (93%)
PP	48/53 (91%)	51/52 (98%)

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.

Data Source: Statistical Tables 1.41 and 1.42 in Section 12, BCC ISE.

7.2.1.6.3 Lesion Response by Location

Lesion CR rates in the PP and ITT population stratified by lesion location are shown in Table 44. There is no indication that location affects response rate to MAL-PDT with response rates ranging from 85% for the trunk and neck and 100% for the extremity in the PP population. It should be noted that lesions in the mid-face were excluded, as these are considered to belong to a high-risk BCC population.

Table 44: Lesion Complete Response Rates by Lesion Location

Active Controlled Study of Nodular BCC (ITT and PP)

Study Location	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	ITT	PP	ITT	PP
303/99				
Face and Scalp	20/22 (91%)	20/21 (95%)	31/32 (97%)	31/32 (97%)
Trunk and Neck	23/27 (85%)	23/27 (85%)	15/16 (94%)	15/15 (100%)
Extremity	5/6 (83%)	5/5 (100%)	5/5 (100%)	5/5 (100%)

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment
Data Source: Statistical Tables 1.41 and 1.42 Section 12, BCC ISE.

7.2.1.6.4 Lesion Response by Size

Table 45 shows the Lesion CR rates stratified by lesion size (ie, largest diameter) in the ITT and PP populations. There is no indication that lesions size affects the response rate to MAL-PDT.

Table 45: Lesion Complete Response Rates by Lesion Size

Active-Controlled Study of Nodular BCC (ITT and PP)

Study Longest diameter (mm)	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	ITT	PP	ITT	PP
303/99				
≤10 mm	28/30 (93%)	28/29 (97%)	33/34 (97%)	33/34 (97%)
>10-20 mm	20/25 (80%)	20/24 (83%)	16/17 (94%)	16/16 (100%)
>20 mm	none	none	2/2 (100%)	2/2 (100%)

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment
Data Source: Statistical Tables 1.41 and 1.42 in Section 12, BCC ISE.

7.2.1.6.5 Lesion Response by Number of Treatments

Table 46 shows the Lesion CR rates stratified by the number of treatments received by each lesion. Very few lesions received either 1 or 3 treatment sessions; therefore, data were grouped as one (1 or 2 sessions) or two (3 or 4 sessions) treatment cycles. The data demonstrate that the overall response rate can be increased by administering a second treatment at 3 months, when the clinical evaluation shows an incomplete response at 3 months.

Table 46: Lesion Complete Response Rates by Number of Treatment Cycles

Active-Controlled Study of Nodular BCC (ITT and PP)

Study No of cycles	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	ITT	PP	ITT	PP
303/99				
1	40/42 (95%)	40/41 (98%)	51/55 (93%)	51/52 (98%)
2	8/13 (62%)	8/12 (67%)		

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment
Data Source: Statistical Tables 1.49 and 1.50 in Section 12, BCC ISE.

7.2.1.6.6 Cosmetic Outcome

Cosmetic Outcome 3 months after Last Treatment

Cosmetic outcome was assessed in all treated patients with a clinical Complete Response 3 months after the last PDT in Study 303/99. Table 47 and Figure 18 (PP only) show patient cosmetic outcome data for the PP and ITT populations. Patients assigned better grades to cosmetic outcomes than did investigators, which is likely because investigators used a standardized cosmetic outcome grading system (see Section 6.2.3), whereas the patients graded subjectively. Despite this difference the outcome with MAL-PDT was clearly superior to excision surgery whether rated by investigators or patients. The majority of patient cosmetic outcomes were rated as ‘excellent’ or ‘good’ for MAL-PDT and the proportion that was rated as excellent cosmetic outcome was significantly higher in the MAL-PDT group, whether rated by investigators or patients.

Cosmetic Outcome at 12 and 24 months after Last Treatment

Table 48 and Figure 18 show the cosmetic outcome at 12 and 24 months after the patient's last treatment in patients who did not have recurrence of their lesion(s) at these time points. Patients continued to assign better grades to cosmetic outcomes than did investigators. MAL-PDT continued to be superior to excision surgery with regards to cosmetic outcome 1 and 2 years after treatment when assessed by investigators as well as patients.

Table 47: Patient Cosmetic Outcome 3 months after last PDT or Surgery

Active-Controlled Study of Nodular BCC (ITT and PP)

Population Outcome	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	Assessor			
303/99	Investigator	Patient	Investigator	Patient
ITT				
Excellent	19/44 (43%)	31/41 (76%)	5/45 (11%)	20/44 (45%)
Excellent 95% CI	28% - 59%	60% - 88%	4% – 24%	30% – 61%
Good	17/44 (39%)	8/41 (20%)	10/45 (22%)	17/44 (39%)
Fair	8/44 (18%)	2/41 (5%)	26/45 (58%)	4/44 (9%)
Poor	0/44 (0%)	0/41 (0%)	4/45 (9%)	3/44 (7%)
PP				
Excellent	19/44 (43%)	31/41 (76%)	5/45 (11%)	20/44 (45%)
Excellent 95% CI	28% - 59%	60% - 88%	4% – 24%	30% – 61%
Good	17/44 (39%)	8/41 (20%)	10/45 (22%)	17/44 (39%)
Fair	8/44 (18%)	2/41 (5%)	26/45 (58%)	4/44 (9%)
Poor	0/44 (0%)	0/41 (0%)	4/45 (9%)	3/44 (7%)

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.

Data Source: Statistical Tables 1.67 and 1.68 in Section 12, BCC ISE.

Table 48: Patient Cosmetic Outcome at 12 and 24 Months

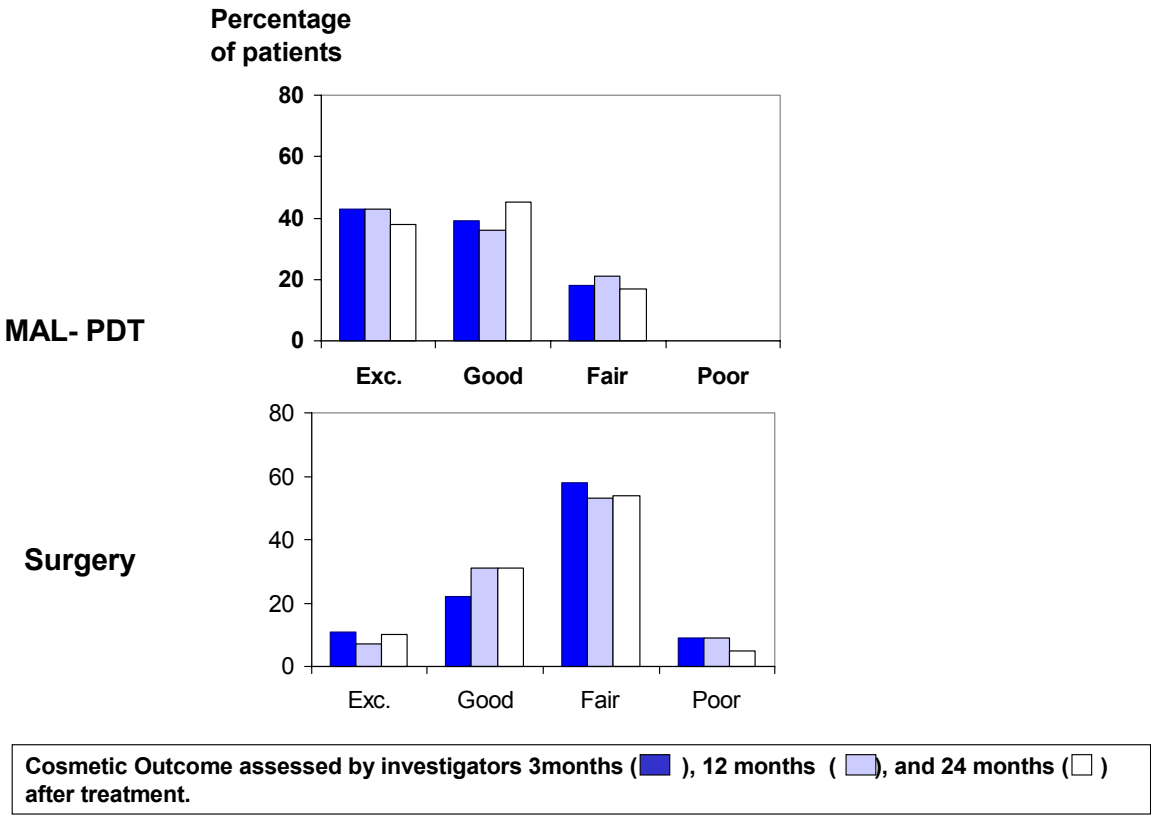
Active-Controlled Study of Nodular BCC (PP)

Period Outcome	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	Assessor			
303/99	Investigator	Patient	Investigator	Patient
12 months				
Excellent	18/42 (43%)	30/42 (71%)	3/45 (7%)	21/43 (49%)
Excellent 95% CI	28% - 59%	55% - 84%	1% - 18%	33% - 64%
Good	15/42 (36%)	11/42 (26%)	14/45 (31%)	15/43 (35%)
Fair	9/42 (21%)	1/42 (2%)	24/45 (53%)	5/43 (12%)
Poor	0/42 (0%)	0/42 (0%)	4/45 (9%)	2/43 (5%)
24 months				
Excellent	11/29 (38%)	20/29 (69%)	4/39 (10%)	14/36 (39%)
Excellent 95% CI	21% - 58%	49% - 85%	3% - 24%	23% - 56%
Good	13/29 (45%)	8/29 (28%)	12/39 (31%)	13/36 (36%)
Fair	5/29 (17%)	1/29 (3%)	21/39 (54%)	8/36 (22%)
Poor	0/29 (0%)	0/29 (0%)	2/39 (5%)	1/36 (3%)

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.

Data Source: Statistical Tables 1.110 and 1.126 in Section 12, BCC ISE.

Figure 18: Cosmetic Outcome, Study 303/99



Cosmetic Outcome assessed by investigators 3months ( ), 12 months ( ), and 24 months ( ) after treatment.

Figure 19: Efficacy of MAL-PDT in Low-Risk Nodular BCC

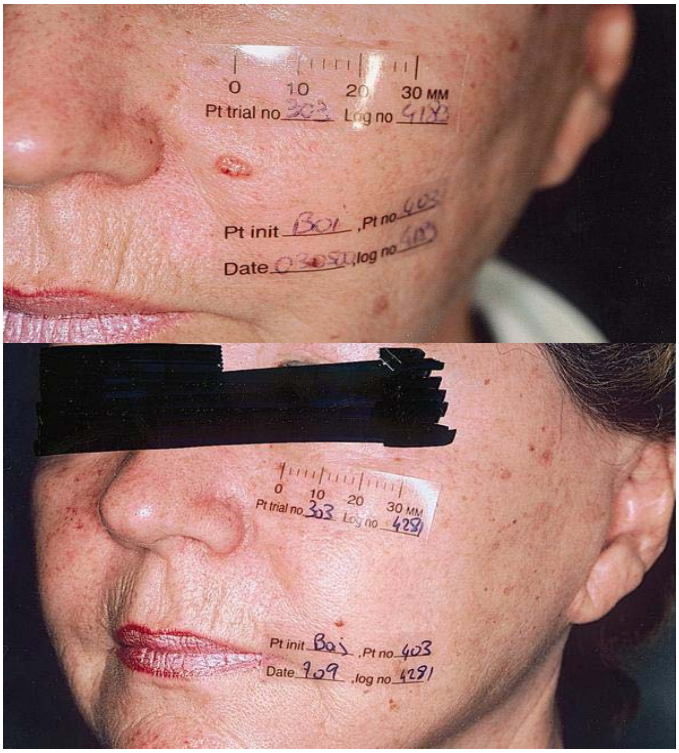


Figure 19: Study 303/99, female, age 65 yrs. Nodular BCC, 6 mm Baseline Complete response, 3 months after treatment with MAL-PDT.

Recurrence Rate

In Study 303/99, lesion recurrence at 12 months was assessed for all lesions in CR at 3 months after the last treatment and lesion recurrence at 24 months was assessed for all lesions that were disease free at 12 months. It should be noted that a patient with a lesion that had failed to show a CR at 3 months might still be included if they had other lesion(s) that were in CR.

Table 49 shows cumulative lesion recurrence data at the 12-month and 24-months time points with and without missing values. Two lesions of 46 lesions recurred at 12 months in the MAL-PDT group and none of the 50 lesions treated by excision surgery. One of the 2 recurrent lesions in the MAL-PDT group was located on the face/scalp and the other on an extremity.

At 24 months there was a further single recurrence in the follow up of 34 lesions in the MAL-PDT group and one recurrence in the population of 44 lesions treated with surgery. Of those treated with MAL-PDT, one was located on the face/scalp and 2 on extremities. The recurrent lesion in the surgery group was on the face/scalp. Thus, recurrence rates up to 2 years are similar in the 2 treatment groups.

Table 49: Lesion Recurrence Rates at the 12 and 24 Month Assessment

Active-Controlled Study of Primary Nodular BCC

Period Study status	MAL-PDT* n/N (%)		Excision Surgery n/N (%)	
	Including missing values	Excluding missing values	Including missing values	Excluding missing values
303/99				
12 months				
Non-Recurrence	44/48 (92%)	44/46 (96%)	50/51 (98%)	50/50 (100%)
Recurrence	2/48 (4%)	2/46 (4%)	0/51 (0%)	0/50 (0%)
Missing	2/48 (4%)		1/51 (2%)	
24 months				
Non-Recurrence	31/48 (65%)	31/34 (91%)	43/51 (84%)	43/44 (98%)
Recurrence	3/48 (6%)	3/34 (9%)	1/51 (2%)	1/44 (2%)
Missing	14/48 (29%)		7/51 (14%)	

* Two sessions of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment

Data Source: Statistical Tables 1.96, 1.97, 1.113 and 1.114 in Section 12, BCC ISE.

7.2.2 Efficacy in Low-Risk Primary Superficial BCC

Study 304/99 was an active-comparator controlled study with patients randomized to cryotherapy or MAL-PDT, performed in Europe.

7.2.2.1 Patient and Lesion Disposition

7.2.2.1.1 Patient Disposition

Table 50 shows the number of patients randomized and treated in Study 304/99 by treatment group. All but 2 patients randomized to receive MAL-PDT were treated and all patients randomized to cryotherapy were treated.

Table 50: Patients Randomized and Treated

Study of Primary Superficial BCC

Study	MAL-PDT* N (%)	Cryotherapy** N (%)	Total N (%)
304/99			
Randomized	62 (52%)	58 (48%)	120 (100%)
Treated	60 (97%)	58 (100%)	118 (98%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Table 2.1 in Section 12, BCC ISE.

7.2.2.1.2 Lesion Disposition

Table 51 shows the number of lesions randomized and treated in Study 304/99 by treatment group. All but 2 lesions randomized to receive MAL-PDT were treated and all patients randomized to cryotherapy were treated.

Table 51: Number of Lesions Randomized and Treated

Study of Primary Superficial BCC

Study	MAL-PDT* N (%)	Cryotherapy** N (%)	Total N (%)
304/99			
Randomized	116 (52%)	105 (48%)	221 (100%)
Treated	114 (98%)	105 (100%)	219 (99%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Table 2.2 in Section 12, BCC ISE.

7.2.2.2 Patient Demography and Baseline Lesion Characteristics

Table 52 shows the age and sex distribution of the 2 treatment groups. They were well matched for age with mean of 63 years in the MAL-PDT group and 64 years in the cryotherapy group. In the MAL-PDT group, there was a preponderance of males with approximately a 2:1 split, whereas in the cryotherapy group the sexes were more evenly balanced. The difference between the groups was not statistically significant.

Table 52: Patient Demography

Study of Primary Superficial BCC (ITT)

Study Variable	MAL-PDT	Cryotherapy	Total	P-value
304/99				
Age (years)	**N=60**	**N=58**	**N=118**	
Mean ± SD	63 ± 16	64 ± 13	64 ± 15	P=0.9023
Median	64	68	66	
Min – Max	25 – 87	38 – 90	25 - 90	
Sex (N, %)				P=0.1091
Male	40 (67%)	30 (52%)	70 (59%)	
Female	20 (33%)	28 (48%)	48 (41%)	

* P-Values for difference in sex distribution between treatment groups is from the CMH test adjusted for centre. P-Values for difference in age are from the ANOVA with factors treatment, center and their interaction.
Data Source: Statistical Table 2.5 in Section 12, BCC ISE.

7.2.2.2.1 Number of Lesions

A total of 219 lesions were included in the ITT population, of which 114 were in the MAL-PDT group and 105 were in the cryotherapy group. Approximately two-thirds of the patients in each group had single lesions and most of the remainder had 2, 3, or 4 lesions. The treatment groups were well matched for number of lesions per patient.

Table 53: Patient Distribution by Number of Lesions per Patient

Study of Primary Superficial BCC (ITT)

Study	Lesions per Patient	Number (%) of Patients			
		MAL-PDT	Cryotherapy	Total	P-value*
304/99	1	39 (65%)	39 (67%)	78 (66%)	0.4791
	2	9 (15%)	8 (14%)	17 (14%)	
	3	6 (10%)	5 (9%)	11 (9%)	
	4	3 (5%)	2 (3%)	5 (4%)	
	5	0 (0%)	1 (2%)	1 (1%)	
	6	0 (0%)	2 (3%)	2 (2%)	
	7	1 (2%)	0 (0%)	1 (1%)	
	10	2 (3%)	1 (2%)	3 (3%)	
	Total	114 (100%)	105 (100%)	118 (100%)	

*P-value is from the CMH test adjusting for center after stratifying lesion number into two categories (1 lesion and ≥2 lesions).
Data Source: Statistical Table 2.13 in Section 12, BCC ISE.

7.2.2.2.2 Location of Lesions

Table 54 shows the location of lesions in the 2 treatment groups. The majority (74%) of superficial lesions occurred on the neck and trunk. As expected, few lesions were located in the face and scalp. The 2 groups were very well matched for distribution of lesions with about three quarters located on the neck and trunk and most of the remainder on the extremities.

Table 54: Locations of Lesions

Study of Primary Superficial BCC (ITT)

Study Location	MAL-PDT N (%)	Cryotherapy N (%)	Total N (%)
304/99	N= 114 lesions	N=105 lesions	N= 219 lesions
Face/Scalp	6 (5%)	6 (6%)	12 (5%)
Neck/Trunk	84 (74%)	78 (74%)	162 (74%)
Extremities	24 (21%)	21 (20%)	45 (21%)

Data Source: Statistical Table 2.17 in Section 12, BCC ISE.

7.2.2.2.3 Lesion Size

Table 55 shows the mean largest lesion diameter per patient in the 2 treatment groups. Lesions were slightly larger in the MAL-PDT than the cryotherapy group (mean 14.4 mm vs 12.8 mm) but the difference is small and not statistically significant.

Table 55: Mean Largest Lesion Diameter per Patient Before Treatment

Study of Primary Superficial BCC (ITT)

Study Variable (mm)	MAL-PDT	Cryotherapy	Total	P-Value*
304/99	N=60	N=58	N=118	
Mean ±SD	14.4 ±5.1	12.8 ±4.7	13.6 ±4.9	Treatment P=0.4499
Median	13.2	11.5	12.9	
Min – Max	7.7 – 30.0	6.0 – 26.0	6.0 – 30.0	

* P-Value for difference between treatment groups in largest lesion diameter per patient is from the ANOVA with factors treatment, center and their interaction.

Data Source: Statistical Tables 2.15 and 2.21in Section 12, BCC ISE.

7.2.2.3 Number of Treatments

Table 56 shows the number of treatment sessions per patient. Patients received just 1 session of PDT initially. About a third of patients required a second treatment because of non-complete response at 3 months. On re-treatment, they received 2 sessions with an interval of one week. In the cryotherapy group, 28% received a second treatment because of non-complete response at 3 months. Cryotherapy was performed with a hand-held liquid nitrogen spray, using a double freeze-thaw cycle. After an initial ice field formation with a 3 mm rim of clinically healthy tissue, the ice field was to be maintained for a minimum of 20 seconds. This procedure was repeated after a thaw of 2-3 times the freeze time.

Table 56: Number of Treatment Sessions per Patient

Active-Controlled Study of Primary Superficial BCC (ITT)

Study Number of treatments	MAL-PDT* N (%)	Cryotherapy** N (%)	Total N (%)
304/99			
1	39 (65%)	42 (72%)	81(69%)
2	0 (0%)	16 (28%)	16 (14%)
3	21 (35%)	0 (0%)	21 (18%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment of two freeze thaw cycles.
Data Source: Statistical Table 2.25 in Section 12, BCC ISE.

Table 57 shows the number of treatment sessions per lesion for the 2 treatment groups. The proportion of lesions requiring a single treatment session is very similar for the 2 treatment modalities.

Table 57: Number of Treatment Sessions per Lesion

Active-Controlled Study of Primary Superficial BCC (ITT)

Study Number of treatments	MAL-PDT* N (%)	Cryotherapy** N (%)	Total N (%)
304/99	**113 lesions**	**105 lesions**	**219 lesions**
1	77 (68%)	73 (70%)	150(68%)
2	0 (0%)	32 (30%)	32 (15%)
3	36 (32%)	0 (0%)	36 (16%)
Total Number of Treatments	184	137	321

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment, of two freeze thaw cycles..
Data Source: Statistical Table 2.23 in Section 12, BCC ISE.

7.2.2.4 Patient Response Rate

In Study 304/99, the lesion and hence patient complete responses were based on clinical assessment by the investigator. Patients were considered to have a complete response if 100% of their lesions showed CR 3 months after their last PDT or cryotherapy. Table 58 shows Patient Clinical Complete Response rates for the ITT and PP populations treated with MAL-PDT or cryotherapy.

Since the study was intended to show non-inferiority of MAL-PDT compared to cryotherapy, the primary analysis was based on the PP population. MAL-PDT was to be considered non-inferior to cryotherapy if it were demonstrated that it was no more than 15% inferior to cryotherapy with respect to patient CR. Therefore, the one-sided upper 97.5% confidence limit for the difference in CR rates was required to be less than 15% in order to conclude that MAL-PDT was non-inferior to cryotherapy. The patient CR rate with MAL-PDT was 95% and that with cryotherapy was 91% resulting in a treatment

difference of 4% in favor of MAL-PDT. The Mantel-Haenszel weighted treatment difference (cryotherapy minus MAL-PDT), accounting for center effects, was -3.4% and the one-sided 97.5% upper confidence limit of the comparison was 5.1%, supporting the hypothesis that MAL-PDT is non-inferior to cryotherapy.

Table 58: Patient Complete Response Rate

Active-Controlled Study of Primary Superficial BCC (PP and ITT)

Study Population	MAL-PDT* n/N (%)	Cryotherapy** n/N (%)	Difference (estimated) MAL – Cryotherapy***
304/99			
PP	55/58 (95%) 95% CI: 86%-99%	52/57 (91%) 95% CI: 81%-97%	-3.40 Upper 97.5% CI: 5.15
ITT	54/60 (90%) 95% CI: 80%-96%	52/58 (90%) 95% CI: 79%-96%	NA

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
*** P-Value from CMH
Data Source: Statistical Tables 2.45, 2.46, 2.51, 2.52 and 2.54 in Section 12, BCC ISE.

7.2.2.5 Lesion Response Rate

Table 59 shows the lesion response rates to MAL-PDT and cryotherapy in the ITT and PP populations. The results are consistent with the patient response rates showing very similar response rates to the 2 treatments, which are 97% lesion response in the PP-population for MAL-PDT and 95% in the ITT population.

Table 59: Lesion Complete Response Rate

Active-Controlled Study of Primary Superficial BCC (ITT and PP)

Study Population	MAL-PDT* n/N (%)	Cryotherapy** n/N (%)
304/99		
ITT	108/114 (95%)	94/105 (90%)
PP	99/102 (97%)	93/98 (95%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Tables 2.41 and 2.42 in Section 12, BCC ISE.

7.2.2.5.1 Lesion Response by Location

Table 60 shows the lesion response rate by location. The lesion response is high in all locations, and there is no indication that the response to either treatment is affected by location.

Table 60: Lesion Complete Response Rates by Lesion Location

Active-Controlled Study of Primary Superficial BCC (ITT and PP)

Study Lesion location	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	ITT	PP	ITT	PP
304/99				
Face/Scalp	6/6 (100%)	6/6 (100%)	3/6 (50%)	3/4 (75%)
Trunk/Neck	79/84 (94%)	71/73 (97%)	71/78 (91%)	71/74 (96%)
Extremity	23/24 (96%)	22/23 (96%)	20/21 (95%)	19/20 (95%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Tables 2.41 and 2.42 in Section 12, BCC ISE.

7.2.2.5.2 Lesion Response by Size

Lesion Complete Response rates, stratified by largest diameter, are shown in Table 61 for the ITT and PP populations. The number of lesions greater than 14 mm diameter is sufficient to indicate that response rates are similar for lesions of all sizes up to 30 mm largest diameter.

Table 61: Lesion Complete Response Rates by Lesion Size

Active-Controlled Study of Primary Superficial BCC (ITT and PP)

Study Lesion size (mm)	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	ITT	PP	ITT	PP
304/99				
5-14	72/76 (95%)	66/68 (97%)	64/74 (86%)	63/67 (94%)
15-19	21/21 (100%)	18/18 (100%)	14/15 (93%)	14/15 (93%)
20-30	14/15 (93%)	14/14 (100%)	16/16 (100%)	16/16 (100%)
> 30	1/2 (50%)	1/2 (50%)		

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Tables 2.41 and 2.42 in Section 12, BCC ISE.

7.2.2.5.3 Lesion Response by Number of Treatments

Table 62 shows the response rates for lesions requiring 1 treatment session only and for those requiring a second treatment after 3 months, which for MAL-PDT consisted of 2 sessions with an interval of 1 week. The response rates for those lesions requiring a

second treatment were not inferior to those requiring one only indicating that administration of a second treatment is worthwhile when needed.

Table 62: Lesion Complete Response Rates by Number of Treatment Cycles

Active-Controlled Study of Primary Superficial BCC (ITT and PP)

Study No of Cycles	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	ITT	PP	ITT	PP
304/99				
1	73/78 (94%)	69/71 (97%)	65/73 (89%)	65/67 (97%)
2	35/36 (97%)	30/31 (97%)	29/32 (91%)	28/31 (90%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions (ie, one cycle) of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Table 2.43 and 2.44 in Section 12, BCC ISE.

7.2.2.6 Cosmetic Outcome

Cosmetic outcome in Study 304/99 was assessed in all treated patients with a clinical Complete Response. Table 63 shows patient cosmetic outcome data for the PP and ITT population. Patients assigned somewhat better grades to cosmetic outcomes than did investigators. The ratings after MAL-PDT were clearly superior to those after cryotherapy. It is apparent that the proportion rated as 'excellent' cosmetic outcome was far higher in the MAL-PDT than in the cryotherapy group whether rated by investigators (PP population: 30% vs. 4%) or patients (PP-population: 45% vs. 20%).

Table 63: Patient Cosmetic Outcome 3 months after last MAL-PDT or Cryotherapy

Active-Controlled Study of Primary Superficial BCC (ITT and PP)

Population Outcome	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	Assessor			
304/99	**Investigator**	**Patient**	**Investigator**	**Patient**
ITT				
Excellent	17/53 (32%)	22/46 (48%)	2/50 (4%)	9/44 (20%)
Excellent 95% CI	20% - 46%	33% - 63%	1% - 14%	10% - 35%
Good	30/53 (57%)	24/46 (52%)	23/50 (46%)	24/44 (55%)
Fair	6/53 (11%)	0/46 (0%)	25/50 (50%)	11/44 (25%)
PP				
Excellent	16/53 (30%)	21/47 (45%)	2/50 (4%)	9/44 (20%)
Excellent 95% CI	18% - 44%	30% - 60%	1% - 14%	10% - 35%
Good	31/53 (58%)	26/47 (55%)	23/50 (46%)	24/44 (55%)
Fair	6/53 (11%)	0/47 (0%)	25/50 (50%)	11/44 (25%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.
** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.
Data Source: Statistical Tables 2.55, 2.56, 2.57 and 2.58 in Section 12, BCC ISE.

Cosmetic Outcome at 12 and 24 months

Table 64 shows the cosmetic outcome at 12 and 24 months after the patient's last treatment in patients who did not have recurrence of their lesion(s) at these time points. Patients continued to assign somewhat better grades to cosmetic outcomes than did investigators. There was some improvement in cosmetic outcome in the MAL-PDT group compared to outcomes assessed 3 months after last treatment. In the PP population, investigator 'excellent' outcomes were 39% at 12 months and 56% at 24 months for MAL-PDT and 14% and 8% respectively in the cryotherapy group. MAL-PDT continued to be superior to cryotherapy with regards to cosmetic outcome 1 year and 2 years after treatment when assessed by investigators as well as patients.

Table 64: Patient Cosmetic Outcome at 12 and 24 Months

Active-Controlled Study of Primary Superficial BCC (PP)

Period Outcome	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	Assessor			
304/99	Investigator	Patient	Investigator	Patient
12 months				
Excellent	17/44 (39%)	18/42 (43%)	6/43 (14%)	12/40 (30%)
Excellent 95% CI	24% - 54%	28% - 59%	5% - 28%	17% - 46%
Good	22/44 (50%)	24/42 (57%)	20/43 (47%)	21/40 (53%)
Fair	5/44 (11%)	0/42 (0%)	17/43 (40%)	7/40 (18%)
24 months				
Excellent	19/34 (56%)	17/33 (52%)	3/38 (8%)	11/33 (33%)
Excellent 95% CI	38% - 73%	33% - 69%	2% - 21%	18% - 52%
Good	12/34 (35%)	16/33 (48%)	15/38 (39%)	17/33 (52%)
Fair	3/34 (9%)	0/33 (0%)	20/38 (53%)	5/33 (15%)

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT.

** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy.

Data Source: Statistical Tables 2.94, 2.96, 2.111 and 2.113 in Section 12, BCC ISE.

7.2.2.7 Recurrence Rate

In Study 304/99, lesion recurrence at 12 months was assessed for all lesions in CR at 3 months after the last treatment and lesion recurrence at 24 months was assessed for all lesions that were disease free at 12 months. It should be noted that a patient with a lesion that had failed to show a CR at 3 months might still be included if they had other lesion(s) that were in CR.

Table 65 shows lesion recurrence data at the 12-month and 24-months time points with and without missing values. In both populations at 12 months, there were recurrences in 10 of 108 lesions (9%) in the MAL-PDT group and 12 of 94 lesions (13%) in the cryotherapy group. At 24 months including missing values, there were recurrences in 18 of 108 lesions (17%) in the MAL-PDT group and 19 of 94 (20%) in the cryotherapy group. The corresponding figures for the population excluding missing values were 17 of 91 (19%) and 19 of 88 (22%), for MAL-PDT and cryotherapy, respectively.

Table 65: Lesion Recurrence Rates at 12 and 24 Month Assessment

Active-Controlled Study of Primary Superficial BCC

Period Status	MAL-PDT* n/N (%)		Cryotherapy** n/N (%)	
	Missing values included	Missing values excluded	Missing values included	Missing values excluded
304/99				
12 months				
Non-Recurrence	97/108 (90%)	89/98 (91%)	80/94 (85%)	79/91 (87%)
Recurrence	10/108 (9%)	9/98 (9%)	12/94 (13%)	12/91 (13%)
Missing	1/108 (1%)		2/94 (2%)	
24 months				
Non-Recurrence	82/108 (76%)	74/91 (81%)	70/94 (74%)	69/88 (78%)
Recurrence	18/108 (17%)	17/91 (19%)	19/94 (20%)	19/88 (22%)
Missing	8/108 (7%)		5/94 (5%)	

* One session of MAL-PDT. After 3 months, lesions with non-CR received 2 additional sessions of PDT treatment.

** One session of cryotherapy. After 3 months, lesions with non-CR received one additional cryotherapy treatment.

Data Source: Statistical Tables 2.80, 2.81, 2.97 and 2.98 in Section 12, BCC ISE.

7.3 Efficacy in High-Risk BCC (Unsuitable for Conventional Therapy)

Two non-comparative studies were performed in patients with superficial and nodular BCC unsuitable for conventional therapy (high-risk BCC). Study 205/98 was performed in Europe and Study 310/00 was performed in Australia.

7.3.1 Patient and Lesion Disposition

In Study 205/98, 94 patients were included and treated and in Study 310/00, 102 patients were included and treated making a total population of 196 patients.

In Study 205/98 123 lesions were included and treated; 14 lesions were treated although they were subsequently regarded as non-eligible by an independent study review board. In Study 310/00 187 lesions were included of which 165 were treated; the difference being due to lesions not confirmed as eligible on biopsy. A total of 288 nodular and superficial high-risk BCC lesions were treated in these 2 studies.

7.3.2 Patient Demography and Baseline Characteristics

The populations were of similar age, mean 68 years in Europe and 64 years in Australia, and the split of sexes, with a preponderance of about two-thirds males, is very similar in the two populations.

7.3.2.1 Number of Lesions

In Study 205/98 most of the patients (87%) had one lesion, and in Study 310/00 69% of the patients had 1 lesion and 18% had 2 lesions.

7.3.2.2 Lesion Type

Table 66 shows the types of lesion included in these 2 studies. Lesions of nodular, superficial and mixed forms are represented in each of the studies. In Study 205/98, there were approximately equal numbers of nodular and superficial lesions and there were few mixed forms. In Study 310/00, more than half the lesions were superficial; nodular and mixed forms were equally represented.

Table 66: Lesion Types

Studies of BCC Unsuitable for Conventional Therapy (ITT)

Study Lesion Type	N (%)
205/98	
Nodular	58 (47%)
Superficial	55 (45%)
Mixed form	7 (6%)
Non-BCC	3 (2%)
310/00	
Nodular	36 (22%)
Superficial	92 (56%)
Mixed form	37 (22%)
Non-BCC	0 (0%)

Data Source: Statistical Table 3.15 in Section 12, BCC ISE.

7.3.2.3 Location of Lesions

Table 67 shows the location of lesions. In Study 205/98, more than half of the lesions were located on the face/scalp. In Study 310/00, the distribution of lesions on face/scalp and neck/trunk are similar, the difference between the studies probably reflecting the greater proportion of nodular lesions in Study 205/98 which are known to occur more frequently on face and scalp.

Table 67: Locations of Lesions

Studies of BCC Unsuitable for Conventional Therapy (ITT)

Study Location	MAL-PDT N (%)
205/98	N=123 lesions
Face/Scalp	74 (60%)
Neck/Trunk	32 (26%)
Extremities	17 (14%)
310/00	N=165 lesions
Face/Scalp	62 (38%)
Neck/Trunk	70 (42%)
Extremities	33 (20%)

Data Source: Statistical Table 3.13 in Section 12, BCC ISE.

7.3.2.4 Lesion Size

Table 68 shows the distribution of lesion size based on their largest lesion diameter before treatment. The mean largest diameters are similar in the 2 studies 20 mm in Europe and 17.5 mm in Australia, but there were some much larger lesions in the European study.

Table 68: Largest Lesion Diameter (mm) per Patient Before Treatment

Studies of BCC Unsuitable for Conventional Therapy (ITT)

Study Characteristic	MAL-PDT
205/98	No. of Patients =94
Mean ± SD	23.4 ± 17.8
Median	20.0
Min – Max	5.0 – 110.0
310/00	No. of Patients =102
Mean ± SD	20.3± 11.6
Median	17.5
Min – Max	3.0 – 62.0

Data Source: Statistical Table 3.11 in Section 12, BCC ISE.

7.3.2.5 Number of Treatments

Table 69 shows the number of treatment sessions per patient. Each cycle consisted of two treatments with an interval of 1 week. A second cycle was administered if the response after 3 months was non-complete. Therefore, almost all patients had either 2 sessions or four. In both studies, similar (about a third) number of patients required re-treatment after 3 months.

Table 69: Number of PDT Sessions per Patient

Studies of BCC Unsuitable for Conventional Therapy (ITT)

Study	Number of Sessions	MAL-PDT N (%)
205/98	1	1 (1%)
	2	55 (59%)
	3	1 (1%)
	4	37 (39%)
	Total	94 (100%)
310/00	1	1 (1%)
	2	69 (68%)
	3	0 (0%)
	4	32 (31%)
	Total	102 (100%)

* One cycle of MAL-PDT treatment (i.e. 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Table 3.19 in Section 12, BCC ISE.

7.3.3 Patient Response Rate

All complete response rates refer to responses verified by histological examination of punch biopsies of the treated area taken 3 months after the last PDT. Patients were considered to have a complete response if all of their lesions showed clinical and histological complete response.

Table 70 shows the complete response rates for the ITT and PP populations for Studies 205/98 and 310/00. Based on the ITT populations, the patient complete response rates for MAL-PDT were 72% (95% CI: 62% to 81%) and 80% (95% CI: 71% to 88%) respectively.

These results allowed the rejection of the null hypothesis (Study 205/98: fair/excellent/complete response rate of MAL-PDT ≤50%; Study 310/00: Complete response rate of MAL-PDT ≤65%) in favor of the alternative hypothesis (Study 205/98: fair/excellent/complete response rate of MAL-PDT >50%; Study 310/00 >65% (see also Section 6.2.6).

Table 70: Patient Complete Response Rate

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study	MAL-PDT* n/N (%)	
	ITT	PP
205/98	68/94 (72%) 95% CI: 62% - 81%	61/85 (72%) 95% CI: 61% - 81%
310/00	82/102 (80%) 95% CI: 71% - 88%	81/95 (85%) 95% CI: 76% - 92%

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Tables 3.45 and 3.46 in Section 12, BCC ISE.

7.3.4 Lesion Response Rate

Table 71 shows lesion complete response rates with histological verification of response for the ITT and PP populations in Studies 205/98 and 310/00. Based on the ITT populations, the lesion complete response rates for MAL-PDT were 75% in Study 205/98 and 85% in Study 310/00 respectively. Individual lesion complete response rates are slightly greater than patient complete response rates because some patients had more than one lesion and all lesions within a patient may not have shown CR.

Table 71: Lesion Complete Response

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study	MAL-PDT* n/N (%)	
	ITT	PP
205/98	92/123 (75%)	80/108 (74%)
310/00	141/165 (85%)	131/148 (89%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Tables 3.35 and 3.36 in Section 12, BCC ISE.

7.3.4.1 Lesion Response by Type

Table 70 shows lesion complete response rates by lesion type with histological verification of response for the ITT and PP populations in Studies 205/98 and 310/00. Based on the ITT populations, the highest lesion response was seen for superficial lesions with 80% in Study 205/98 and 91% in Study 310/00. The response rates for nodular lesions in the ITT populations for the 2 studies are virtually identical, 74% response rate in the European study and 75% in the Australian study.

Table 72: Lesion Complete Response by Lesion Type

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study / Lesion type	MAL-PDT* n/N (%)	
	ITT	PP
205/98		
Nodular	43/58 (74%)	38/52 (73%)
Superficial	44/55 (80%)	39/49 (80%)
Mixed form	3/7 (43%)	3/7 (43%)
Non-BCC	2/3 (67%)	
310/00		
Nodular	27/35 (75%)	27/33 (82%)
Superficial	84/92 (91%)	74/80 (93%)
Mixed form	30/37 (81%)	30/35 (86%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Tables 3.33 and 3.34 in Section 12, BCC ISE.

7.3.4.2 Lesion Response by High-Risk Criterion at Inclusion

Specific criteria were used to define the lesions as high-risk (Section 6.2). In Study 310/00, by comparing the lesion response rates by these individual criteria, it was found that the response rates did not markedly differ between the individual high-risk criteria used (Table 73).

Table 73: Lesion Response by High Risk Criterion at Inclusion, Lesion Description and Location (Study 310/00)

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study / High Risk Criterion	MAL-PDT*					
	ITT			PP		
	Number of lesions	CR	Non-CR	Number of lesions	CR	Non-CR
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
310/00						
No HR lesion, no surgical risk	5 (3)	3 (60)	2 (40)	-	-	-
H zone	32 (19)	27 (84)	5 (16)	31 (21)	26 (84)	5 (16)
Large lesion	91 (55)	77 (85)	14 (15)	82 (55)	72 (88)	10 (12)
Large lesion in H zone	16 (10)	13 (81)	3 (19)	15 (10)	13 (87)	2 (13)
Neither large nor in H zone	1 (9)	1 (100)	0 (0)	1 (1)	1 (100)	0 (0)
Only surgical risk	20 (19)	20 (100)	0 (0)	19 (13)	19 (100)	0 (0)
Total	165 (100)	141 (85)	24 (15)	148 (100)	131 (89)	17 (11)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.

Data Source: Study 310/00 study report tables 55 and 58.

7.3.4.3 Lesion Response by Location

Lesion complete response rates stratified by lesion location are shown for both the ITT and PP populations in Table 74. Response rates are slightly greater on the trunk/neck and extremities than on the face/scalp. Nevertheless, the lesion complete response rate histological verified was at least 69% at all locations in both studies and all populations. It should be noted that most facial lesions in these studies were located in the mid-face or H-zone.

Table 74: Lesion Complete Response by Lesion Location

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study / Lesion location	MAL-PDT* n/N (%)	
	ITT	PP
205/98		
Face/Scalp	51/84 (69%)	45/65 (69%)
Trunk/Neck	26/32 (81%)	22/28 (79%)
Extremity	15/17 (88%)	13/15 (87%)
310/00		
Face/Scalp	48/62 (77%)	46/57 (81%)
Trunk/Neck	63/70 (90%)	57/61 (93%)
Extremity	30/33 (91%)	28/30 (93%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.

Data Source: Statistical Tables 3.31 and 3.32 in Section 12, BCC ISE.

7.3.4.4 Lesion Response by Size

Lesion complete response rates by largest diameter, are shown in Table 75 for the ITT and PP populations. Since, by definition, large lesions were considered unsuitable for conventional therapy, these studies include a substantial number of the largest lesions. In both studies it is clear that the response rates of these lesions are similar to those of small lesions and response rates are independent of lesion size.

Table 75: Lesion Complete Response by Lesion Size

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study **Lesion size (mm)**	**MAL-PDT*** **n/N (%)**	
	ITT	**PP**
205/98		
Missing	1/1 (100%)	1/1 (100%)
< 5	2/2 (100%)	1/1 (100%)
5-14	32/44 (73%)	26/36 (72%)
15-19	10/14 (71%)	9/12 (75%)
20-30	21/29 (72%)	18/26 (69%)
> 30	26/33 (79%)	25/32 (78%)
310/00		
< 5	2/3 (67%)	2/3 (67%)
5-14	49/56 (88%)	46/51 (90%)
15-19	24/31 (77%)	23/29 (79%)
20-30	45/50 (90%)	40/42 (95%)
> 30	21/25 (84%)	20/23 (87%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Tables 3.31 and 3.32 in Section 12, BCC ISE.

7.3.4.5 Lesion Response by Number of Treatments

Lesion complete response rates by the number of treatment cycles received by each lesion are shown in Table 76. As with patient response, the lesion response rate is lower in lesions requiring a second treatment cycle but more than 50% of lesions showing a non-complete response to the first cycle showed a complete response to the second cycle, which is clearly worthwhile. The results are consistent between the 2 studies.

Table 76: Lesion Complete Response by Number of PDT Cycles

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study Number of Cycles	MAL-PDT* n/N (%)	
	ITT	PP
205/98		
1	68/79 (86%)	57/66 (86%)
2	24/44 (55%)	23/42 (55%)
310/00		
1	120/127 (94%)	112/115 (97%)
2	21/38 (55%)	19/33 (58%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.
Data Source: Statistical Tables 3.37 and 3.38 in Section 12, BCC ISE.

7.3.5 Cosmetic Outcome

Table 77 presents the lesion cosmetic outcomes at 3 months after the last MAL-PDT treatment for patients in the ITT and PP populations with a biopsy-confirmed complete response. In both studies cosmetic outcome was rated 'excellent' or 'good' for the majority of lesions. In Study 205/98, the investigator considered that 28% of patients had an excellent cosmetic outcome, whereas in Study 310/00, approximately 50% of patients were considered to have an excellent cosmetic outcome by the investigator. Patients in both studies assigned slightly higher grades to cosmetic outcomes than the investigators, with approximately 50% considering the outcome 'excellent' and almost all the remainder considering it 'good'. Neither investigators nor patients graded any cosmetic response 'poor'. These cosmetic results are highly satisfactory in view of the fact that these lesions are generally unsuitable for conventional therapy because of their size and the disfigurement that may result from other therapies, such as surgery.

Table 77: Patient Cosmetic Outcome 3 months after last PDT

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study Outcome	MAL-PDT* n/N (%)			
	ITT		PP	
	Assessor		Assessor	
	Investigator	Patient	Investigator	Patient
205/98				
Excellent	18/67 (27%)	26/55 (47%)	17/60 (28%)	24/51 (47%)
Excellent 95% CI	17% - 39%	34% - 61%	17% - 41%	33% – 61%
Good	34/67 (51%)	25/55 (45%)	29/60 (48%)	23/51 (45%)
Fair	15/67 (22%)	4/55 (7%)	14/60 (23%)	4/51 (8%)
310/00				
Excellent	37/81 (45%)	40/81 (49%)	37/79 (47%)	41/79 (52%)
Excellent 95% CI	35% - 57%	38% - 61%	35% - 58%	40% - 63%
Good	16/81 (20%)	39/81(48%)	15/79 (19%)	36/79 (46%)
Fair	28/81 (35%)	2/81 (2%)	27/79 (34%)	2/79 (3%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.

Data Source: Statistical Tables 3.49, 3.50, 3.51 and 3.52 in Section 12, BCC ISE.

Cosmetic Outcome at 12 and 24 months

Table 78 shows the cosmetic outcome at 12 and 24 months in the PP population after the patient's last treatment in patients who did not have a recurrence of their lesion(s) at these time points. The 24-month data available comprise only the investigator assessment in Study 205/98. Overall, there was slight improvement in cosmetic outcome between the 3-month and the 12-month assessments.

Table 78: Patient Cosmetic Outcome at 12 and 24 Months

Studies of BCC Unsuitable for Conventional Therapy (PP)

Study Period Outcome	MAL-PDT* n/N (%) Assessor	
	Investigator	**Patient**
205/98		
12 months		
Excellent	19/60 (32%)	36/58 (62%)
95% CI	*20% – 45%*	*48% – 74%*
Good	32/60 (53%)	18/58 (31%)
Fair	8/60 (13%)	4/58 (7%)
Poor	1/60 (2%)	0/58 (0%)
24 months		
Excellent	23/48 (48%)	
95% CI	*33% – 63%*	Not Applicable
Good	22/48 (46%)	
Fair	2/48 (4%)	
Poor	1/48 (2%)	
310/00		
12 months		
Excellent	33/72 (46%)	
95% CI	*34% - 58%*	Not Applicable
Good	24/72 (33%)	
Fair	14/72 (19%)	
Poor	1/72 (1%)	

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.

Data Source: Statistical Tables 3.95, 3.97, 3.99 and 3.101 in Section 12, BCC ISE.

7.3.6 Recurrence Rate

Recurrence of lesions in complete response at 3 months after the last MAL-PDT treatment was assessed at 6 months in Study 205/98 and 12 months for both Study 205/98 and Study 310/00 and then annually. Follow up is planned for 5 years; currently data are available for 24 months after treatment in Study 205/98 and for 12 months after treatment in Study 310/00. Recurrence of lesions was based on clinical assessment (inspection and palpation) confirmed by punch biopsy, if recurrence was suspected.

Table 79 shows the histologically verified cumulative lesion recurrence rates for Studies 205/98 and 310/00. Of lesions that had a complete response at 3 months after the last MAL-PDT treatment, 7 to 9% had recurred 12 months after treatment (PP-population). At this time point, recurrence rates were similar in the two studies. In Study 205/98, all lesions that recurred within 12 months were in the largest original size category (>30 mm longest diameter) and situated on the trunk or extremities (where the highest proportion

of large lesions was situated). However, in Study 310/00 there was no apparent relation between size or lesion location and recurrence rate.

The numbers of lesions followed up to 24 months (Study 205/98 only) after treatment is smaller, but a further 5 lesions recurred during the second year of follow-up. The recurrence rate in this time-period was not related to size or location of lesions.

Table 79: Lesion Recurrence Rates at the 12 and 24 Month Assessment

Studies of BCC Unsuitable for Conventional Therapy (ITT and PP)

Study Period Status	MAL-PDT* n/N (%)	
	ITT	**PP**
205/98		
12 months		
Non-Recurrence	69/92 (75%)	69/80 (86%)
Recurrence	7/92 (8%)	7/80 (9%)
Missing	16/92 (17%)	4/80 (5%)
24 months		
Non-Recurrence	54/92 (59%)	54/66 (82%)
Recurrence	12/92 (13%)	12/66 (18%)
Missing	26/92 (28%)	
310/00		
12 months		
Non-Recurrence	122/141 (87%)	113/121 (93%)
Recurrence	9/141 (6%)	8/121 (7%)
Missing	10/141 (7%)	0/121 (0%)

* One cycle of MAL-PDT treatment (ie, 2 sessions separated by one week). After 3 months, lesions with PR (205) or non-CR (310) received one additional cycle of MAL-PDT treatment.

Data Source: Statistical Tables 3.73, 3.74, 3.75 and 3.76 in Section 12, BCC ISE.

7.4 Discussion

7.4.1 Response Rate and Cosmetic Outcome in Low-Risk Nodular BCC

The two placebo-controlled studies provide unequivocal and consistent evidence of the efficacy of MAL-PDT in nodular BCC. It is apparent that the response rates to MAL-PDT and placebo-PDT are somewhat higher in Study 307/00 than in Study 308/00. The reason for this is not apparent though it is possibly related to the fact that a greater proportion of patients had a second cycle of treatment at three months. However, the mean differences between CR rates to active and placebo in the two studies are very similar at 42% and 49% for the ITT populations of Studies 307/00 and 308/00 respectively. The similarity of results of these two studies, one of which was performed in the United States and the other in Australia, provides support for the relevance of foreign data for this NDA.

The magnitude of the response to placebo-PDT is perhaps surprisingly high. It is not likely that illumination with non-coherent light of wavelength 570 –670 nm could have any effect per se. It is presumably due to the procedures associated with treatment,

especially the lesion preparation prior to cream application. The histology results showed an inflammatory reaction in all of the lesions, irrespective of treatment indicating that this is due to the biopsy / preparation procedures. Almost all lesions were prepared before each illumination.

It should be noted that patients with an apparent clinical response of less than 50% were not retreated in the placebo-controlled studies. In total, 22 lesions were excised after 3 months, seven in the MAL-PDT group. The response rate to MAL-PDT after two treatments and hence the overall response may be an underestimate of what can be achieved clinically since it is possible that some of these lesions would have shown complete response after a second cycle of treatment. Furthermore, it cannot be assumed that the presence of residual cells in excised skin from the treated area would necessarily result in recurrence of the tumor. The true cure rate can only be established by long-term follow-up of treated lesions (see below).

The clinically assessed patient response rate of 87% to MAL-PDT in the active comparator (surgery)-controlled trial in the ITT population is similar to the clinical response in the placebo-controlled studies (80% and 82%). Study 303/99 was performed in Europe, again showing the consistency of outcome in studies performed in different continents. The statistical analysis, based on the more conservative PP population for the comparison between surgery and MAL-PDT using the pre-defined criterion for non-inferiority of 15% difference, shows MAL-PDT to be non-inferior to simple excision surgery. Recurrence in the first 2 years post-treatment seemed to be slightly more frequent in the MAL-PDT group.

Perhaps of greater importance than the small differences in response rates, is the clear superiority in cosmetic outcome with MAL-PDT whether assessed by investigators or patients. For nodular lesions, which so frequently occur on the face and cosmetically sensitive areas, the superior tissue-conserving ability of MAL-PDT is an important clinical advantage for this treatment.

7.4.2 Response Rate and Cosmetic Outcome in Low-Risk Superficial BCC

The lesion response rates to MAL-PDT in the active-comparator Study 304/99 were equal to or greater than 95% and were similar to (slightly higher than) those for cryotherapy. Lesions up to 30 mm largest diameter showed similar response rates to those of smaller lesions. Recurrence rates with MAL-PDT and cryotherapy were similar.

As with nodular BCC, the cosmetic outcome with MAL-PDT in superficial BCC was clearly superior to that of cryotherapy. The greatest drawback with cryotherapy is hypopigmentation that persists. Although this does occur with MAL-PDT, it is much less common and is generally rated as mild. Some persistent redness is not uncommon but scarring and tissue defects are very infrequent. Superficial lesions occur frequently on the legs and the importance of a good tissue preservation and cosmetic outcome should not be underestimated.

7.4.3 Comparison of Response Rate between Studies in Low-Risk Superficial and Nodular BCC

Studies 307/00, 308/00, 303/99, and 304/99 were all conducted in patients with low-risk BCC lesions.

The patient complete response rates with MAL-PDT in the comparative clinical trials in nodular and superficial BCC (Studies 303/98 and 304/98) were 87% and 90% respectively and the corresponding Lesion Complete Response rates were 87% and 95% respectively.

The patient complete response rates in the placebo-controlled studies of MAL-PDT (Studies 307/00 and 308/00) in nodular BCC were somewhat lower at 76% and 67% respectively, and the lesion response rates were 78% and 68% respectively. This may partly reflect the different method of assessment, since in the placebo-controlled studies the area affected was completely excised and subjected to detailed histological examination, whereas in the active comparator studies the assessment was based on clinical examination. If remaining tumor cells were inevitably to lead to recurrence, the complete response rate found by thoroughly examining serial histological sections should correspond to the final disease-free rate. This is conservative since it has not been shown that all remaining cells would develop into a tumor. Most likely, this is not the case, since it is known that remaining tumor cells after surgery only in less than 50% of cases will develop into a new tumor.[15]

An additional explanation of the lower response rates in Studies 307/00 and 308/00 is that, as mentioned above (Section 7.4.1), patients with an apparent clinical response of less than 50% were not retreated in the placebo-controlled studies for ethical reasons. As a result, fewer lesions received a second treatment cycle in the placebo-controlled studies. Results from the active controlled studies indicate that some of the lesions with less than a 50% response would have shown a complete response after re-treatment.

7.4.4 Response to Re-treatment

For nodular BCC, the response rates were increased by giving a second cycle of treatment after 3 months when lesions had failed to show a complete response after the first cycle. The response rate was somewhat lower after the second cycle suggesting that these lesions are more aggressive and less response to MAL-PDT overall. Nevertheless, it is clearly worthwhile to administer a second course of treatment when required.

Unlike nodular BCC, response rates for those superficial lesions requiring a second treatment were not inferior to those requiring one only. It should be noted that two-thirds of lesions showed a complete response to one session of MAL-PDT only. It seems likely that the response rate to the first treatment would have been higher and fewer lesions would have required re-treatment if a cycle of two PDT sessions had been given initially. Two sessions of PDT for the initial cycle as well as for retreatment when required are recommended.

7.4.5 Response Rate and Cosmetic Outcome in High-Risk BCC (Unsuitable for Conventional Therapy)

Management of patients with superficial and nodular high-risk BCC lesions that are recurrent, large, invasive, or are located in the H-zone of the face or ear varies considerably between different centers and no satisfactory standard conventional therapy is recognized. The majority of lesions were in these studies were considered high-risk BCC because of their size or location. The overall patient response rate with MAL-PDT in Study 205/98 at 3 months was 72% and the lesion response rate was 74%. It is generally desirable to compare an investigational treatment with an active comparator, but this was not possible since tumors were selected for the very reason that they were unsuitable for traditional therapy due to high risk of complications and poor cosmetic outcome associated with poor tissue preservation. Despite the lack of an active comparator or placebo control, which was precluded on ethical grounds, this study provides unequivocal evidence of efficacy of the standard regimen of MAL-PDT applied as one or, if required, two cycles of treatment in the management of BCC lesions unsuitable for conventional therapy.

The results in the more recent Study 310/00 performed in Australia support those of the European study. The response rates were slightly higher with patient and lesion response rates of 80% and 85% respectively. The difference might be due to chance, but the fact that three patients with only ‘low-risk’ lesions and, in total, 20 ‘low-risk’ lesions were included may have contributed slightly. However, these patients were eligible because they were at high risk of morbidity from surgery or irradiation and the results therefore reflect the response rates with MAL-PDT that can be expected in a patient population unsuitable for other treatment modalities. All of the lesions that were included based on surgical risk factors responded completely and there were no recurrences after 12 months.

It is interesting that the response rates in these lesions after one or two treatments are of a similar magnitude to those in the primary or ‘low-risk’ lesions and it should be noted that the responses were all confirmed histologically by punch biopsy. While biopsy cannot be as comprehensive as complete excision of the affected area as performed in Studies 307/00 and 308/00, it suggests that initial response rates may not be inferior to those of ‘low-risk’ lesions.

There are no obvious patient demographic factors, such as sex, age or skin type, that affect response rates. With regard to lesion factors, size, depth or location of the lesion do not appear to influence the initial response rate. In Study 205/98 the 12-month recurrence rate appeared to increase with increasing lesion diameter, however, this was not confirmed by Study 310/00, where lesion size had no influence on recurrence rate. The only consistent finding of a factor that is associated with the overall response rate is the lesion response itself to the first treatment cycle, which is higher than for lesions requiring a second cycle of treatment, at least for nodular lesions. Nevertheless, most lesions will show a complete response after a second treatment cycle leaving a small number of treatment failures after 6 months. Since most tumors are slow growing and almost all show at least a partial response, it is worth administering a second course of treatment and no harm will result if treatment fails. Importantly, since MAL-PDT does

lead to scars or changes in the structure of the skin or tissues, treatment with MAL-PDT does not preclude any other alternative therapeutic modalities.

The excellent cosmetic results seen with 'low-risk' lesions have even greater importance to 'high-risk' patients. The lesions are destructive and treatment may interfere with function of vital structures. Prolonged and sometimes repeated surgery including Mohs surgery is not only hazardous in this elderly population but results in loss of large areas of tissue since wide margins must be taken to maximize the chances of complete tumor removal. Extensive surgical resection requires flap or graft reconstruction from which considerable disfigurement is inevitable. By contrast, MAL-PDT, which does not affect normal skin because of its high selectivity, poses virtually no risk of disfigurement or loss of function. Recurrent lesions may already have adverse cosmetic signs resulting from previous treatment and MAL-PDT will avoid further tissue damage in such situations. Cosmetic results in lesions showing a complete response after a second cycle were similar to those requiring only one treatment cycle and appear to improve for at least a year following treatment. Hence, the treatment can be repeated.

Figure 20: Efficacy of MAL-PDT in High-Risk Nodular BCC

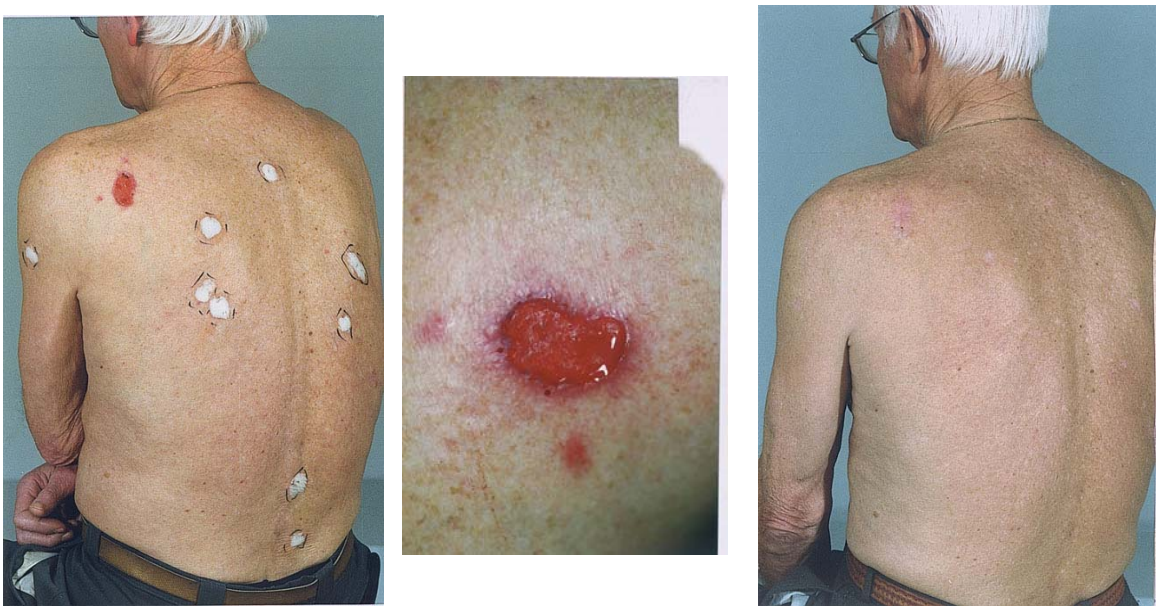


Figure 20: Study 205/98, patient 104, male, age 74. Lesion 1: Nodular BCC, 33 mm. Left and middle panel show lesion after preparation, before cream application. Right panel shows the result 3 months post-treatment.

Non-complete response after 3 months, re-treated. Complete response 3 months after the second MAL-PDT cycle. Sustained response 36 months post-treatment.

Figure 21: Efficacy of MAL-PDT in High-Risk Mixed Type BCC

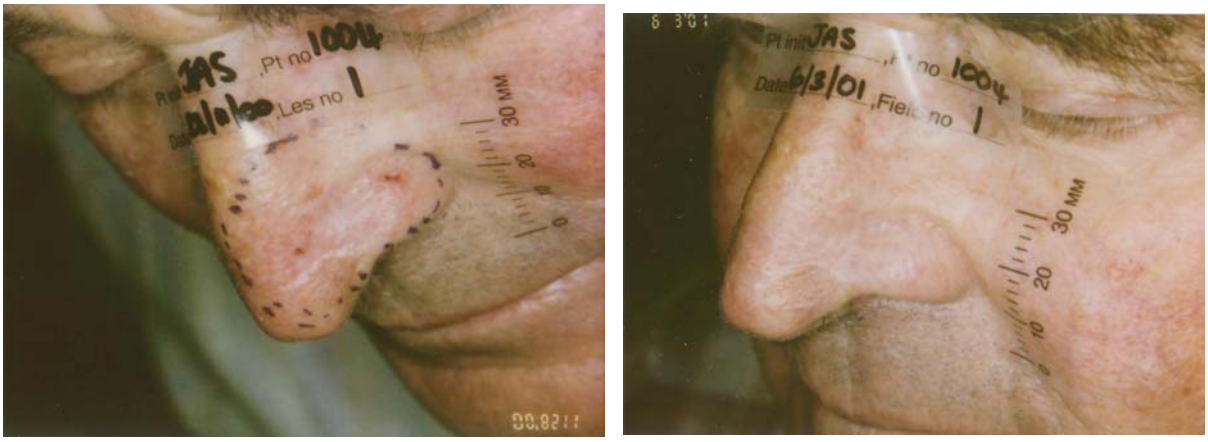


Figure 21: Study 310/00. Patient 1004, male age 63. Mixed type lesion, 35 mm. Complete response after one treatment cycle.

7.5 Conclusion

In conclusion, photodynamic therapy using MAL 168 mg/g Cream applied for 3 h before illumination with non-coherent light with a total fluence of 75 J/cm^2 is an effective treatment for nodular and superficial basal cell carcinoma.

Response rates and 24-month recurrence rates for low-risk (primary) lesions are similar to those with excision surgery and cryotherapy. Response rates are not related to the size of the lesion or its location or to patient age, sex or skin type. Satisfactory response and recurrence rates are also obtained in lesions of a 'high-risk' category not suitable for conventional therapy and in patients at high risk of morbidity from surgery.

A treatment cycle of two sessions with an interval of one week is recommended. Response rates on re-treatment of nodular lesions failing to show a complete response after 3 months are somewhat lower than to the first treatment. However, it is clearly worthwhile to retreat nodular as well as superficial lesions when required since more than 50% of lesions show a complete response on re-treatment.

For both nodular and superficial lesions, the proportion of patients and lesions with Excellent / Good ratings of cosmetic outcome by investigators and patients are consistently high and superior to those of surgery or cryotherapy respectively. The cosmetic results in patients with lesions unsuitable for conventional therapy, many of which are located on the face and ears were also highly satisfactory. The high rates of Excellent / Good cosmetic outcome are attributable to tissue conservation with MAL-PDT. This avoids disfigurement and interference with function of vital structures, which are commonly associated with surgery, particularly in the mid-face.

Thus, in both low-risk and high-risk superficial and nodular BCC, treatment with MAL-PDT achieves the 3 main clinical objectives of BCC treatment, namely to remove the tumor, conserve as much healthy tissue as possible, preserve tissue function, and avoid disfigurement.

8 EVALUATION OF SAFETY

8.1 Safety Assessments

8.1.1 Analysis Populations

Safety analyses were performed using the intent-to-treat (ITT) population only. The definition of the ITT population was the same as that used in the individual studies: all patients randomized to treatment who received at least 1 dose of randomized study medication or who underwent at least 1 of the other interventions planned for the comparator group belonged to the ITT population.

8.1.2 Coding of Adverse Events

Concomitant medication data were coded according to the Anatomic Therapeutic Chemical (ATC) classification and summarized by treatment using counts of patients.

All AEs were coded according to their World Health Organization (WHO) preferred term using the WHOART dictionary (Version 8.99). All AEs were classified as either local or non-local.

In all studies, local AEs were defined as all AEs that were classified as associated with the WHO organ class of "Skin and Appendages Disorders." After November 2001, a sponsor-defined system organ class field was added to the dictionary, so that local phototoxicity events that had previously been classified as non-local, such as application site reaction and tingling skin, were classified as local.

To provide a good description of AEs relating to phototoxicity, some additional codes were generated to describe AEs for which there are no WHO codes. These events were as follows:

- Bleeding skin;
- Burning sensation skin;
- Crusting;
- Erosion;
- Hypopigmentation;
- Pustule;
- Edema skin;
- Irritability skin;
- Pain skin;

- Stinging skin; and
- Suppuration.

8.1.3 Adverse Event Definitions

Numbers of AEs and numbers of patients with AEs were summarized by treatment using counts and percentages of AEs or patients. Separate summaries were produced for local and non-local AEs. Total numbers of AEs represent unique AE terms.

Adverse events were summarized by their severity and relationship to treatment. Severity and relationship to treatment were assessed in the same way in all studies. If the same preferred term was reported more than once by the same patient, the highest level of severity was reported. A response of "Uncertain" or "Yes" with respect to relationship to treatment was categorized as "related" to treatment, while a response of "No" was categorized as "not related." Duration of related local AEs assessed as moderate or severe was calculated and summarized by mean, standard deviation (SD), median, minimum, and maximum.

Serious adverse events were considered to be any untoward medical occurrence that resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a congenital anomaly or birth defect. In most studies, except in the follow-up phase of the long-term follow-up BCC studies, SAEs were reported in an expedited manner, if they fulfilled 1 of the above criteria.

Duration of related local AEs assessed as moderate or severe was calculated and summarized by mean, SD, median, minimum, and maximum.

Anesthesia was explicitly allowed as a concomitant medication in Studies 307/00 and 308/00; it was permitted in the other studies when the investigator felt that it was necessary. Local anesthetics were used for some patients in Studies 205/98, 303/99, 304/99, 307/00, 308/00, and 310/00, but were not used by any patients in Studies 101/97, 203/98, and 206/98. For studies in BCC, the number of patients who used local anesthesia was determined. The use of local anesthesia (yes/no) was used to stratify data on the number of patients with non-local and local AEs. In addition, the number of patients experiencing specific local AEs was also stratified by use of local anesthesia.

By-patient listings were produced for deaths, other SAEs, discontinuations due to AEs, and instances when treatments were stopped because of AEs.

During the follow-up periods of most studies, AE data were not collected, but information about patient withdrawals from the study due to AEs was collected.

8.1.4 Clinical Laboratory Evaluations

In studies 101/97, 202/98, 203/98, 204/98, and 205/98, blood samples for laboratory analysis were taken. The following parameters have been measured in all the studies: hemoglobin, alanine transaminase (ALT), aspartate transaminase (AST), and bilirubin.

The following additional laboratory parameters were measured in certain studies: Study 101/97 – platelets, leukocytes, erythrocyte sedimentation rate, creatinine, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), sodium, and potassium; Study 204/98 – creatinine, white blood cells (WBC), and thrombocytes; Study 205/98 – creainine, platelets, and WBC; Studies 202/98 and 203/98 – WBC and thrombocytes.

In connection with the AK NDA (21-415), the FDA requested additional analyses of clinical data on liver enzymes. The laboratory parameters ALT, AST, and bilirubin from Studies 202/98 and 203/98 were used to evaluate the change in liver function tests from baseline to 4 to 9 days after 1 PDT session. Differences between treatment groups who were treated with different cream concentrations and application times were also analyzed. The laboratory parameters ALT, AST, and bilirubin from Study 205/98 were used to evaluate the change in liver function tests from baseline to 4 to 9 days after 2 PDT sessions, using a dose of 168 mg/g methyl aminolevulinate and an application time of 3 hours. These data were also used to evaluate the difference between 2 and 4 PDT sessions with a dose of 168 mg/g methyl aminolevulinate and an application time of 3 hours.

Local laboratories with different reference ranges for the specific laboratory parameters were used in each study. The reference ranges also differ between males and females. To standardize the laboratory data between centers and genders, the change from before PDT to after PDT was presented as a percentage of the size of the reference range. Increases or decreases of more than 40% of the reference range are commented on in the analyses below.

A typical reference range in these studies was 10 to 50 U/L for ALT and AST and 3 to 26 μmol/L for bilirubin. For these reference ranges, an increase of more than 40% of the reference range means an increase of more than 16 U/L for ALT or AST, and for bilirubin an increase of more than 9.2 μmol/L. These increases are intentionally conservative, since a clinically relevant increase in these laboratory parameters is often defined as an increase of more than 2 times the upper reference limit, which means an increase of more than 100 U/L for ALT and AST and 52 μmol/L for bilirubin.

8.2 Overall Safety Results

This section of the briefing document summarizes the safety results for all patients treated with methyl aminolevulinate-PDT in prospective clinical studies of this treatment in BCC and AK. The following studies are included: 101/97, 203/98, 205/98, 303/99, 304/99, 307/00, 308/00, and 310/00 in BCC; 202/98, 204/98, 301/99, 302/99, 305/99, and 306/99 in AK; and 206/98 in BCC and AK. The comparator treatment is not presented. However, safety results for the comparator treatments in the individual studies are presented in Sections 8.3 and 8.4.

8.2.1 Patient Demographics and Disposition

Patient disposition and demographic are summarized in Table 80. A total of 940 patients were randomized in these studies, 546 with BCC and 394 with AK. Almost all

randomized patients (98%) were treated, and 94% of randomized patients completed the study. Completion rates were similar in patients with AK (96%) and patients with BCC (92%). The BCC studies had a follow-up period of up to 24 months, while patients with AK were followed for 3 months.

The most common reason for discontinuation was AEs, followed by lost to follow-up, consent withdrawn, and reasons classified as "Other." Only 9 of all AEs associated with discontinuation were regarded as related to treatment. Of these, 2 were noted as having an uncertain relationship to treatment. All 9 events resolved.

Table 80: Patient Disposition and Demographic Characteristics in Studies in BCC and AK

Variable	Patients with BCC n (%)	Patients with AK n (%)	Total n (%)
Patients randomized	546	394	940
Patients treated (ITT population)	538 (99)	383 (97)	921 (98)
Patients completed study	494 (92)	369 (96)	863 (94)
Patients discontinued	44 (8)	14 (4)	58 (6)
Age (years)			
Mean (SD)	66 (14)	69 (11)	67 (13)
Median	68	71	69
Minimum, maximum	25, 95	31, 91	25, 95
Sex: n (%)			
Male	327 (61)	241 (63)	568 (62)
Female	211 (39)	142 (37)	353 (38)
Race: n (%)			
Caucasian	374 (70)	251 (66)	625 (68)
Unknown	164 (30)	132 (34)	296 (32)
Other	0	0	0

Source: Statistical Tables 1.1, 1.2, and 1.3, BCC ISS.

8.2.2 Number of Lesions Per Patient

Numbers of lesions per patient are summarized for studies in BCC and AK in Table 81. Lesion distribution was typical for these conditions. Patients with BCC had fewer lesions than patients with AK; the majority (73%) of patients with BCC had 1 lesion. The majority (68%) of patients with AK had 1 to 4 lesions, while 8 (2%) of these patients had more than 10 lesions. No patient with BCC had more than 10 lesions.

Table 81: Number of Lesions per Patient in Studies in BCC and AK
ITT Population, Patients Treated with Methyl Aminolevulinate Only

Number of lesions per patient	Patients with BCC N = 538 n (%)	Patients with AK N = 383 n (%)	Total N = 921 n (%)
1	393 (73)	78 (20)	471 (51)
2	65 (12)	65 (17)	130 (14)
3	38 (7)	67 (17)	105 (11)
4	22 (4)	54 (14)	76 (8)
5	8 (1)	33 (9)	41 (4)
6	5 (1)	27 (7)	32 (3)
7	1 (0)	18 (5)	19 (2)
8	2 (0)	11 (3)	13 (1)
9	1 (0)	11 (3)	12 (1)
10	3 (1)	11 (3)	14 (2)
11-28	0	8 (2)	8 (1)

Source: Statistical Table 1.6, BCC ISS.

8.2.3 Exposure

8.2.3.1 Number of Treatments Per Lesion

A total of 2362 lesions have been treated in the studies of BCC and AK. Numbers of treatments per lesion are summarized in Table 82. The number of treatments per lesion was determined primarily by the details of the study design of each protocol. Most BCC lesions (83%) and all AK lesions received 1 or 2 treatments.

Table 82: Number of Treatments per Lesion in Studies in BCC and AK
ITT Population, Patients Treated with Methyl Aminolevulinate Only

Number of treatments per lesion	Patients with BCC N = 857 lesions n (%)	Patients with AK N = 1505 lesions n (%)	Total N = 2362 lesions n (%)
0	1 (0)	0	1 (0)
1	358 (42)	750 (50)	1108 (47)
2	348 (41)	755 (50)	1103 (47)
3	41 (5)	0	41 (2)
4	109 (13)	0	109 (5)

Source: Statistical Table 1.7, BCC ISS.

8.2.3.2 Number of Treatment Visits Per Patient

Numbers of visits per patient were determined primarily by the study designs, as described in the different study protocols. Most patients with BCC and all but 1 patient with AK had 1 or 2 treatment visits.

8.2.3.3 Cream Application Time and Illumination Variables

There were no significant differences in cream application time and illumination variables between the BCC and the AK studies. Overall, the mean (SD) application time was 3:16 (2:05) (h:min), the mean illumination time was 9:58 (3:43) (min:sec), the mean light intensity was 141 (44) mW/cm^2, the mean light dose was 76 (9) J/cm^2 and the mean light field diameter was 42 (12) mm.

8.2.4 Overview of Adverse Events

Treatment-emergent AEs in studies in BCC and AK are summarized in Table 83. Seventy-nine percent of patients had 1 or more AE, for a total of 2219 events. Overall, incidences of AEs were similar in patients with BCC and patients with AK. A total of 36 (4%) patients had 1 or more SAE (only 1 SAE, burning sensation in skin, was considered related to treatment). The incidence of SAEs was 5% in patients with BCC and 3% in patients with AK. Nineteen patients died; the death rate was higher in patients with BCC than in patients with AK (none was related to treatment). However, in general, patients with BCC were followed for 24 months, while patients with AK were followed for 3 months. Thirty-two patients discontinued because of AEs (3 noted as discontinuing because of intercurrent disease), including 24 patients with BCC and 8 patients with AK. However, only 9 of these AEs were regarded as related to treatment. Of these, 2 were noted as having an uncertain relationship to treatment. All 9 events resolved.

Table 83: Summary of Treatment-Emergent Adverse Events in Studies in BCC and AK

ITT Population, Patients Treated with Methyl Aminolevulinate Only

Variable	Patients with BCC N = 538	Patients with AK N = 383	Total N = 921
Patients with any AE: n (%)	434 (81)	297 (78)	731 (79)
Number of AEs: n	1422	797	2219
Patients who died: n	18	1	19
Patients with any SAE: n (%)	26 (5)	10 (3)	36 (4)
Number of SAEs: n	33	12	45
Patients discontinuing because of AEs: n	22	7	29

Source: Statistical Tables 1.14, 1.22, 1.2, BCC ISS.

The incidence of local and non-local AEs is summarized in Table 84. Approximately 75% of patients experienced local AEs. Incidence of local AEs was similar in patients with BCC and patients with AK. Similar percentages of patients in the 2 groups had 1, 2, and 3-4 local AEs (22%, 18%, and 23%, respectively). The incidence of non-local AEs was lower than that of local AEs, and was similar in patients with AK (22%) and in patients with BCC (27%). Most patients who had non-local AEs had only 1 such event.

Table 84: Overview of Local and Non-Local Adverse Events in Studies in BCC and AK

ITT Population, Patients Treated with Methyl Aminolevulinate Only

	Patients with BCC N = 538 n (%)	Patients with AK N = 383 n (%)	Total N = 921 n (%)
Patients with any local AE	405 (75)	282 (74)	687 (75)
No. of local AEs			
1	114 (21)	90 (23)	204 (22)
2	83 (15)	80 (21)	163 (18)
3-4	127 (24)	85 (22)	212 (23)
5-6	69 (13)	25 (7)	94 (10)
7-10	12 (2)	2 (1)	14 (2)
Patients with any non-local AE	146 (27)	83 (22)	229 (25)
No. of non-local AEs			
1	90 (17)	57 (15)	147 (16)
2	35 (7)	21 (5)	56 (6)
3-4	17 (3)	5 (1)	22 (2)
5-6	3 (1)	0	3 (0)
7-10	1 (0)	0	1 (0)

Source: Statistical Table 1.15, BCC ISS.

8.2.4.1 Local Adverse Events

Local AEs that were considered related to treatment are summarized in Table 85. Approximately 73% of patients had such events, and the frequency was similar between patients with BCC and patients with AK. The most frequently occurring event was erythema, which occurred at similar frequencies (about 42%) in the 2 groups of patients. Other frequently occurring events were skin pain (33.8%), burning sensation in the skin (30.6%), skin edema (16.2%), pruritus (13.7%), crusting (11.1%), and stinging skin (10.3%). Skin pain, skin edema, crusting, and stinging skin occurred more frequently in patients with BCC than in patients with AK, while burning sensation in skin occurred more frequently in patients with AK. However, the most frequent local AEs in both groups were expected phototoxic reactions, and, overall, the local AE profiles in the 2 patient populations were similar.

Table 85: Local Adverse Events Related to Treatment Reported by ≥1% of Patients in Studies in BCC and AK

ITT Population, Patients Treated with Methyl Aminolevulinate Only

Local Adverse Event (preferred term)	Patients with BCC N = 538 n (%)	Patients with AK N = 383 n (%)	Total N = 921 n (%)
Any AE	395 (73.4)	278 (72.6)	673 (73.1)
Erythema	224 (41.6)	166 (43.3)	390 (42.3)
Pain skin	202 (37.5)	109 (28.5)	311 (33.8)
Burning sensation skin	134 (24.9)	148 (38.6)	282 (30.6)
Edema skin	106 (19.7)	43 (11.2)	149 (16.2)
Pruritus	77 (14.3)	49 (12.8)	126 (13.7)
Crusting	71 (13.2)	31 (8.1)	102 (11.1)
Stinging skin	70 (13.0)	25 (6.5)	95 (10.3)
Skin ulceration	48 (8.9)	19 (5.0)	67 (7.3)
Blisters	38 (7.1)	18 (4.7)	56 (6.1)
Suppuration	35 (6.5)	6 (1.6)	41 (4.5)
Itching	17 (3.2)	12 (3.1)	29 (3.1)
Skin peeling	15 (2.8)	14 (3.7)	29 (3.1)
Bleeding skin	11 (2.0)	11 (2.9)	22 (2.4)
Tingling skin	13 (2.4)	0	13 (1.4)
Erosion	8 (1.5)	4 (1.0)	12 (1.3)
Skin infection	7 (1.3)	4 (1.0)	11 (1.2)

Source: Statistical Table 1.19, BCC ISS.

The severity of local AEs that were considered related to treatment is summarized in Table 86. Approximately 53% of such events were mild, 37% moderate, and 10% severe. All events reported by ≥1% of the patients, except erosion and skin infection, were reported as mild in most patients and severe in the smallest number of patients. It was only for erosion and skin infection, reported by 12 and 11 patients, respectively, that a moderate severity was more common. For the majority of events, the distribution of severities was similar in patients with BCC and in patients with AK.

The use of methyl aminolevulinate cream 168 mg/g-PDT was associated with acute AEs (expected phototoxic reactions) and AEs of moderate duration. Acute AEs, such as skin pain, burning sensation in skin, stinging skin, and tingling skin, lasted for a median of 1 day or less after therapy. Other AEs that lasted up to approximately 1 week included skin edema, pruritus, itching (BCC only), skin peeling, bleeding skin, and skin infection.

Table 86: Severity of Local Adverse Events Related to Treatment Reported by ≥1% of Patients in Studies in BCC and AK

ITT Population, Patients Treated with Methyl Aminolevulinate Only

Adverse Event (preferred term)	Patients with BCC N = 538 n (% of patients with this AE)			Patients with AK N = 383 n (% of patients with this AE)			Total N = 921 n (% of patients with this AE)		
	Mild	Mod	Sev	Mild	Mod	Sev	Mild	Mod	Sev
Any AE	225 (57.0)	132 (33.4)	38 (9.6)	133 (47.8)	116 (41.7)	29 (10.4)	358 (53.2)	248 (36.8)	67 (10.0)
Erythema	166 (74.1)	53 (23.7)	5 (2.2)	120 (72.3)	42 (25.3)	4 (2.4)	286 (73.3)	95 (24.4)	9 (2.3)
Pain skin	130 (64.4)	53 (26.2)	19 (9.4)	68 (62.4)	31 (28.4)	10 (9.2)	198 (63.7)	84 (27.0)	29 (9.3)
Burning sensation skin	58 (43.3)	65 (48.5)	11 (8.2)	73 (49.3)	61 (41.2)	14 (9.5)	131 (46.5)	126 (44.7)	25 (8.9)
Edema skin	83 (78.3)	22 (20.8)	1 (0.9)	24 (55.8)	17 (39.5)	2 (4.7)	107 (71.8)	39 (26.2)	3 (2.0)
Pruritus	66 (85.7)	9 (11.7)	2 (2.6)	37 (75.5)	11 (22.4)	1 (2.0)	103 (81.7)	20 (15.9)	3 (2.4)
Crusting	50 (70.4)	19 (26.8)	2 (2.8)	22 (71.0)	8 (25.8)	1 (3.2)	72 (70.6)	27 (26.5)	3 (2.9)
Stinging skin	37 (52.9)	29 (41.4)	4 (5.7)	12 (48.0)	12 (48.0)	1 (4.0)	49 (51.6)	41 (43.2)	5 (5.3)
Skin ulceration	35 (72.9)	12 (25.0)	1 (2.1)	6 (31.6)	12 (63.2)	1 (5.3)	41 (61.2)	24 (35.8)	2 (3.0)
Blisters	31 (81.6)	6 (15.8)	1 (2.6)	11 (61.1)	6 (33.3)	1 (5.6)	42 (75.0)	12 (21.4)	2 (3.6)
Suppuration	25 (71.4)	10 (28.6)	0	5 (83.3)	1 (16.7)	0	30 (73.2)	11 (26.8)	0
Itching	15 (88.2)	0	2 (11.8)	6 (50.0)	6 (50.0)	0	21 (72.4)	6 (20.7)	2 (6.9)
Skin peeling	12 (80.0)	3 (20.0)	0	8 (57.1)	6 (42.9)	0	20 (69.0)	9 (31.0)	0
Bleeding skin	9 (81.8)	2 (18.2)	0	6 (54.5)	4 (36.4)	1 (9.1)	15 (68.2)	6 (27.3)	1 (4.5)
Tingling skin	11 (84.6)	2 (15.4)	0	0	0	0	11 (84.6)	2 (15.4)	0
Erosion	1 (12.5)	6 (75.0)	1 (12.5)	2 (50.0)	2 (50.0)	0	3 (25.0)	8 (66.7)	1 (8.3)
Skin infection	1 (14.3)	3 (42.9)	3 (42.9)	1 (25.0)	3 (75.0)	0	2 (18.2)	6 (54.5)	3 (27.3)

Source: Statistical Table 1.19, BCC ISS.

8.2.4.2 Non-local Adverse Events

The incidence of non-local AEs that occurred in at least 1% of patients in studies of BCC and AK is summarized in Table 87. In all studies, local AEs were defined as all AEs that were classified as associated with the WHO organ class of "Skin and Appendages Disorders." For Studies 307/00, 308/00, and 310/00, a sponsor-defined system organ class field was added to the dictionary, so that local phototoxicity events that had previously been classified as non-local, such as application site reaction and tingling skin, were classified as local.

Because the definition of "local" used in all studies except 307/00, 308/00, and 310/00, several of the events shown in Table 87 are local reactions, although they were not classified as such. The AEs tingling skin, skin warm, and application site reaction were most probably local phototoxic reactions.

Overall, 24.8% of patients experienced 1 or more non-local AEs. Incidence of non-local AEs was similar in patients with BCC (27.1%) and in patients with AK (21.4%). All non-local AEs occurred in less than 5% of patients. The most commonly occurring non-local AE was BCC. (BCC was reported as an AE if the patient experienced BCC lesions other than those for which he or she enrolled in the study). Excluding new BCC, elective surgical intervention for skin lesions, and AEs that were local (i.e., tingling skin, skin warm, and application site reaction), only headache and influenza-like symptoms were reported as non-local AEs by ≥1% of patients.

The incidence of severe non-local adverse events was low with only 2 MAL-PDT patients (2.2%) experiencing a severe non-local event that was considered related (evaluated as either "Yes" or "Uncertain") to treatment.

Table 87: Non-Local Adverse Events Reported by ≥1% of Patients in Studies in BCC and AK

ITT Population, Patients Treated with Methyl Aminolevulinate Only

Non-Local Adverse Event (preferred term)	Patients with BCC N = 538 n (%)	Patients with AK N = 383 n (%)	Total N = 921 n (%)
Any AE	146 (27.1)	82 (21.4)	228 (24.8)
Basal cell carcinoma	22 (4.1)	4 (1.0)	26 (2.8)
Surgical intervention	19 (3.5)	3 (0.8)	22 (2.4)
Headache	9 (1.7)	10 (2.6)	19 (2.1)
Tingling skin	7 (1.3)	8 (2.1)	15 (1.6)
Skin warm	10 (1.9)	2 (0.5)	12 (1.3)
Influenza-like symptoms	5 (0.9)	6 (1.6)	11 (1.2)
Application site reaction	4 (0.7)	5 (1.3)	9 (1.0)

Source: Statistical Table 1.20, BCC ISS.

8.2.4.3 Summary

- The safety data on MAL-PDT includes data from 940 patients with 2362 lesions treated.
- Seventy-nine percent of patients had 1 or more AEs, for a total of 2219 events. Overall rates of incidence of AEs were similar in patients with BCC and patients with AK.
- A total of 36 (4%) patients had 1 or more SAEs. The incidence of SAEs was 5% in patients with BCC and 3% in patients with AK. Nineteen patients died; the death rate was higher in patients with BCC than in patients with AK. However, there was a much longer follow-up period in the BCC studies than in the AK studies, and none of the deaths were considered related to treatment. Thirty-two patients discontinued because of AEs, including 24 patients with BCC and 8 patients with AK. However, only 9 of the AEs were considered related to treatment and all resolved.
- Local AEs that were considered related to treatment occurred in approximately 73% of patients, and the frequency was similar in patients with BCC and patients with AK. The most frequently occurring event was erythema, which occurred at similar frequencies (about 42%) in the 2 groups of patients. Other frequently occurring events, also local phototoxic reactions, were skin pain, burning sensation in the skin, skin edema, pruritus, crusting, and stinging skin.
- Approximately 53% of local AEs that were considered related to treatment were mild, 37% moderate, and 10% severe. The distribution of AE severities was similar in patients with BCC and patients with AK.
- Acute AEs, such as skin pain, burning sensation in skin, stinging skin, and tingling skin lasted for a median of 1 day or less after therapy. Other AEs that lasted up to approximately 1 week included skin edema, pruritus, itching (BCC only), skin peeling, bleeding skin, and skin infection. Erythema, crusting, skin ulceration, blisters, and suppuration lasted 1 to 2 weeks. Durations of AEs were similar regardless of the type of skin lesion.
- Most patients who experienced local AEs experienced these events after their first treatment rather than after later treatments.
- The majority of patients (512 of 538) did not receive local anesthesia during treatment with MAL-PDT. The percentage of patients who experienced local AEs did not vary depending on whether they were treated with local anesthesia. Patients treated with local anesthesia had somewhat higher incidences of non-local AEs than patients not treated with local anesthesia.
- Overall, 24.8% of patients reported AEs classified as non-local AEs. All non-local AEs occurred in fewer than 5% of patients. Excluding the occurrence of new BCCs, treatment of new BCCs, and local AEs, only headache and influenza-like symptoms were reported as true non-local AEs by ≥1% of patients. These events are commonly

encountered in an elderly population. Thus, there is no evidence that this treatment is related to any specific systemic AE.

8.3 Placebo-Controlled Studies in Primary Nodular BCC

This section summarizes the safety results for all patients enrolled in Phase III BCC studies that compared the safety and efficacy of methyl aminolevulinate cream 168 mg/g-PDT to placebo cream-PDT in patients with primary nodular BCC (Studies 307/00 and 308/00). The text in this section focuses on the combined data, which allows an assessment of the safety profile of methyl aminolevulinate cream 168 mg/g PDT in patients with primary nodular BCC relative to placebo-PDT.

8.3.1 Patient Demographics and Disposition

Patient disposition is summarized in Table 88. A total of 131 patients were randomized in the placebo-controlled studies in primary nodular BCC. All of the patients who were randomized were treated with either methyl aminolevulinate cream 168 mg/g-PDT or placebo-PDT. A minimum of 97% of patients completed the study in each treatment group. A total of 3 patients discontinued from the studies: 1 patient withdrew consent, 1 patient withdrew due to an AE (not related), and 1 patient was lost to follow-up. In addition, 1 patient in the methyl aminolevulinate cream 168 mg/g-PDT treatment in 307/00 continued until 6 months after treated, but had treatment permanently stopped due to the AEs of skin irritability and stinging skin. The mean age±SD of all patients in placebo-controlled primary nodular BCC studies was 66±13 years. All of the patients in these studies were Caucasian. The sex ratio was 76% male and 24% female. The age, sex, and race of patients in the 2 placebo-controlled primary nodular BCC studies did not differ significantly.

Table 88: Patient Disposition and Demographics in Placebo-Controlled Studies in Primary Nodular BCC

Variable	Methyl aminolevulinate-PDT n (%)	Placebo-PDT n (%)	Total n (%)
Patients randomized	66	65	131
Patients treated (ITT population)	66 (100)	65 (100)	131 (100)
Patients completed study	64 (97)	64 (98)	128 (98)
Patients discontinued prematurely	2 (3)	1 (2)	3 (2)
Age (years)			
Mean (SD)	66 (13)	67 (12)	66 (13)
Median	67	68	68
Minimum, maximum	28, 88	39, 88	28, 88
Sex: n (%)			
Male	47 (71)	52 (80)	99 (76)
Female	19 (29)	13 (20)	32 (24)
Race: n (%)			
Caucasian	66 (100)	65 (100)	131 (100)

Source: Statistical Tables 2.1, 2.2, BCC ISS.

8.3.2 Number of Lesions per Patient

Table 89 summarizes the number of lesions per patient in placebo-controlled studies of primary nodular BCC. In total, 150 lesions were treated in these studies; 75 lesions in the MAL-PDT group and 75 lesions in the placebo-PDT group. Overall, 89% of patients had 1 lesion, 8% had 2 lesions, 2% had 3 lesions, and 1% had 4 lesions. The number of lesions per patient was similar in the treatment groups.

Table 89: Number of Lesions per Patient in Placebo-Controlled Studies in Primary Nodular BCC

	ITT Population		
Number of lesions per patient	Methyl aminolevulinate-PDT N = 66 n (%)	Placebo-PDT N = 65 n (%)	Total N = 131 n (%)
1	60 (91)	57 (88)	117 (89)
2	4 (6)	6 (9)	10 (8)
3	1 (2)	2 (3)	3 (2)
4	1 (2)	0	1 (1)

Source: Statistical Table 2.7, BCC ISS.

8.3.3 Exposure

8.3.3.1 Number of Treatments Per Lesion

Table 90 summarizes the number of PDT treatments per lesion in placebo-controlled studies of primary nodular BCC. Overall, 78% of lesions were treated twice, 21% were treated 4 times, and 1% were treated once. The proportion of lesions treated 2 times with PDT was higher in the placebo-PDT treatment group (83%) than in the MAL-PDT (73%) treatment group. This is due to the fact that more lesions in the placebo group than in the methyl aminolevulinate group were partial responders after the first treatment cycle and therefore (per protocol) received a second placebo-PDT treatment.

The number of treatments per lesion varied in the placebo-controlled studies of primary nodular BCC. A higher percentage of lesions in Study 308/00 received only 1 treatment cycle (2 PDT treatments) (86%) as compared with Study 307/00 (71%). Thus, there was a similar shift in the percentages of lesions that received a second treatment cycle at 3 months (4 PDT treatments in total), 13% for Study 308/00 compared with 28% for Study 307/00.

Table 90: Number of Treatments per Lesion in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Number of treatments per lesion	Methyl aminolevulinate-PDT N = 75 lesions n (%)	Placebo-PDT N = 75 lesions n (%)	Total N = 150 lesions n (%)
1	2 (3)	0	2 (1)
2	55 (73)	62 (83)	117 (78)
4	18 (24)	13 (17)	31 (21)

Source: Statistical Table 2.8, BCC ISS.

8.3.3.2 Number of Visits Per Patient

The number of treatment visits was specified in the protocols. In both studies, lesions were to be treated twice, separated by an interval of 1 week. If the 3-month assessment found that a lesion had a PR to treatment, the 2-session treatment was repeated. Overall, most patients (78%) made 2 treatment visits. The proportion of patients treated during 1 or 4 visits was similar in the 2 treatment groups.

8.3.3.3 Cream Application Time and Illumination Variables

Characteristics of exposure were very similar in the 2 treatment groups. The total mean application time was 3:04±0:08 hours:minutes, with a median of 3:00 hours:minutes. Cream application was followed by a mean illumination time of 9:28±3:29 minutes:seconds and a median of 8:20 minutes:seconds. The average total light dose was 77±4 J/cm^2; the median light dose was 77 J/cm^2.

8.3.4 Overview of Adverse Events

Table 91 summarizes the AE incidence and numbers of AEs for patients treated with methyl aminolevulinate cream 168 mg/g-PDT and patients treated with placebo-PDT. As expected, due to known local phototoxic reactions after treatment with methyl aminolevulinate cream 168 mg/g-PDT, the proportion of patients treated with methyl aminolevulinate cream 168 mg/g-PDT with AEs (91%) was higher than the proportion of patients treated with placebo-PDT with AEs (66%). One patient in the methyl aminolevulinate cream 168 mg/g-PDT treatment group died (not related). A total of 2 SAEs (not related) were reported by patients treated with methyl aminolevulinate cream 168 mg/g-PDT, compared to 7 SAEs reported by patients treated with placebo-PDT. One patient in the methyl aminolevulinate cream 168 mg/g-PDT treatment group discontinued the study because of an AE (not related); another patient in the methyl aminolevulinate cream 168 mg/g-PDT treatment group stopped treatment due to AEs (treatment site irritation and stinging sensation at the treatment site), but did not discontinue from the study.

At study entry, 11% (15/131) of patients in placebo-controlled studies of primary nodular BCC were experiencing clinical symptoms. Eight percent of patients in the methyl aminolevulinate cream 168 mg/g-PDT and 11% of patients in the placebo-PDT treatment groups were experiencing 1 clinical symptom; the remainder had 2 clinical symptoms. The single most common clinical symptom at study entry was erythema, reported in 3.1% of all patients, followed by itching in 2.3% of patients. The only other clinical symptoms reported by ≥1% of all patients at entry were coughing and skin pain, each reported by 1.5% of patients.

Table 91: Summary of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Variable	Methyl aminolevulinate-PDT N = 66	Placebo-PDT N = 65	Total N = 131
Patients with any AE: n (%)	60 (91)	43 (66)	103 (79)
Number of AEs: n	175	97	272
Patients who died: n	1	0	1
Patients with any SAE: n (%)	2 (3)	4 (6)	6 (5)
Number of SAEs: n	2	7	9
Patients discontinuing because of AEs: n	1	0	1

Source: Statistical Table 2.16, 2.26, 2.2, BCC ISS.

Table 92 shows an overview of the number of patients with local and non-local AEs in placebo-controlled studies of primary nodular BCC.

In general, patients treated with placebo-PDT reported fewer local and non-local AEs than patients treated with methyl aminolevulinate cream 168 mg/g-PDT. This is discussed further in the following sections.

Among patients with local AEs in the methyl aminolevulinate cream 168 mg/g-PDT group, most reported 1 (27%), 2 (21%), or 3 (21%) events. The profiles of patients in the 2 treatment groups differed: 9% of patients in the placebo-PDT treatment group reported more than 2 AEs, while 26% of patients in the methyl aminolevulinate cream 168 mg/g-PDT treatment group reported between 3 and 10 AEs. The distributions of non-local events per patient were similar in patients treated with methyl aminolevulinate cream 168 mg/g-PDT and placebo-PDT. This provides evidence to support the claim that treatment with methyl aminolevulinate cream 168 mg/g-PDT does not have a systemic effect on patients.

Table 92: Overview of Local and Non-Local Adverse Events in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

	Methyl aminolevulinate-PDT N = 66	Placebo-PDT N = 65	Total N = 131
Patients with any local AE	49 (74)	30 (46)	79 (60)
No. of local AEs			
1	18 (27)	15 (23)	33 (25)
2	14 (21)	9 (14)	23 (18)
3 to 4	14 (21)	6 (9)	20 (15)
5 to 6	1 (2)	0	1 (1)
7 to 10	2 (3)	0	2 (2)
Patients with any non-local AE	38 (58)	28 (43)	66 (50)
No. of non-local AEs			
1	24 (36)	18 (28)	42 (32)
2	8 (12)	7 (11)	15 (11)
3 to 4	5 (8)	2 (3)	7 (5)
5 to 6	1 (2)	1 (2)	2 (2)

Source: Statistical Table 2.17, BCC ISS.

The proportion of patients who experienced local AEs differed in Studies 307/00 and 308/00 (75% and 45%, respectively). This difference is not surprising, given that 4 treatment visits (the maximum) were made by 28% of patients in Study 307/00 versus 14% of patients in Study 308/00. In addition, 28% of patients in Study 307/00 experienced 3 or more local AEs, compared to 8% of patients in Study 308/00.

8.3.4.1 Local Adverse Events

In the majority of cases, local AEs were considered related to study treatment. Therefore, only related local AEs are presented here.

Table 93 shows the incidence of local AEs considered related to study treatment and reported by ≥1% of all patients. The local AEs considered related to treatment in 10% or more of patients who were treated with methyl aminolevulinate cream 168 mg/g-PDT were burning sensation in skin, erythema, skin pain, and stinging skin. The incidences of

related local AEs were, as expected, higher in patients treated with methyl aminolevulinate cream 168 mg/g-PDT than in patients treated with placebo-PDT. Burning sensation in skin was the most common related local AE in both treatment groups (12.3% of patients in placebo-PDT treatment group; 28.8% of patients in methyl aminolevulinate cream 168 mg/g-PDT treatment group).

Table 93: Local Adverse Events Related to Treatment Reported by ≥1% of All Patients in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Local AE (preferred term)	Methyl aminolevulinate-PDT N = 66 n (%)	Placebo-PDT N = 65 n (%)	Total N = 131 n (%)
Any AE	42 (63.6)	20 (30.8)	62 (47.3)
Burning sensation skin	19 (28.8)	8 (12.3)	27 (20.6)
Erythema	14 (21.2)	4 (6.2)	18 (13.7)
Skin pain	12 (18.2)	3 (4.6)	15 (11.5)
Stinging skin	10 (15.2)	5 (7.7)	15 (11.5)
Crusting	5 (7.6)	3 (4.6)	8 (6.1)
Itching	3 (4.5)	2 (3.1)	5 (3.8)
Pruritus	2 (3.0)	3 (4.6)	5 (3.8)
Bleeding skin	4 (6.1)	0	4 (3.1)
Scar	2 (3.0)	2 (3.1)	4 (3.1)
Warm skin	2 (3.0)	2 (3.1)	4 (3.1)
Peeling skin	3 (4.5)	0	3 (2.3)
Application site reaction	2 (3.0)	0	2 (1.5)
Hyperpigmentation skin	0	2 (3.1)	2 (1.5)
Skin irritability	2 (3.0)	0	2 (1.5)

Source: Statistical Table 2.21, BCC ISS.

As would be expected from the differences in the numbers of PDT treatments per patient in the 2 studies, fewer patients had related local AEs in Study 308/00 (21/66, 31.8%) than in Study 307/00 (41/65, 63.1%). There were some differences in the rank orders of individual local AEs; however, the overall constellations of local phototoxic results were similar in these 2 placebo-controlled studies of primary nodular BCC. As mentioned before, local AEs were usually considered related to study treatment. Therefore, only the severities of local events considered related to study treatment are presented here.

Table 94 shows the severity of local AEs related to study treatment and reported by ≥1% of all patients. None of the local events related to study treatment were considered severe. The majority (52.4%) of events related to methyl aminolevulinate cream 168 mg/g-PDT treatment were mild; 70% of events related to placebo-PDT treatment were mild. In the placebo-PDT treatment, there were only a few cases of moderate burning sensation in skin, erythema, stinging skin, itching, and pruritus. These related local AEs may have been caused by lesion preparation procedures. In the methyl aminolevulinate cream

168 mg/g-PDT treatment group, the following related local AEs were moderate and were reported by >1 patient: burning sensation in skin, erythema, skin pain, stinging skin, and crusting.

Table 94: Severity of Local Adverse Events Related to Treatment Reported by ≥1% of All Patients in Placebo-Controlled Studies in Primary Nodular BCC ITT Population

Adverse Event (preferred term)	Methyl aminolevulinate-PDT N = 66 n (%)		Placebo-PDT N = 65 n (%)		Total N = 131 n (%)	
	Mild	Moderate	Mild	Moderate	Mild	Moderate
Any AE	22 (52.4)	20 (47.6)	14 (70.0)	6 (30.0)	36 (58.1)	26 (41.9)
Burning sensation skin	9 (47.4)	10 (52.6)	6 (75.0)	2 (25.0)	15 (55.6)	12 (44.4)
Erythema	8 (57.1)	6 (42.9)	3 (75.0)	1 (25.0)	11 (61.1)	7 (38.9)
Skin pain	4 (33.3)	8 (66.7)	3 (100)	0	7 (46.7)	8 (53.3)
Stinging skin	7 (70.0)	3 (30.0)	3 (60.0)	2 (40.0)	10 (66.7)	5 (33.3)
Crusting	3 (60.0)	2 (40.0)	3 (100)	0	6 (75.0)	2 (25.0)
Itching	3 (100)	0	1 (50.0)	1 (50.0)	4 (80.0)	1 (20.0)
Pruritus	2 (100)	0	2 (66.7)	1 (33.3)	4 (80.0)	1 (20.0)
Bleeding skin	3 (75.0)	1 (25.0)	0	0	3 (75.0)	1 (25.0)
Scar	2 (100)	0	2 (100)	0	4 (100)	0
Warm skin	2 (100)	0	2 (100)	0	4 (100)	0
Peeling skin	2 (66.7)	1 (33.3)	0	0	2 (66.7)	1 (33.3)
Application site reaction	1 (50.0)	1 (50.0)	0	0	1 (50.0)	1 (50.0)
Hyperpigmentation skin	0	0	2 (100)	0	2 (100)	0
Skin irritability	1 (50.0)	1 (50.0)	0	0	1 (50.0)	1 (50.0)

Note: Only mild and moderate severity are shown because there were no related local AEs assessed as severe in this population.
Note: The denominator is the total number of patients in each treatment reporting each AE.
Source: Statistical Table 2.21, BCC ISS.

More moderate related local AEs were reported in Study 307/00 (46.3%) than in Study 308/00 (33.3%). In both studies, a majority of related local AEs occurred in the MAL-PDT treatment group.

8.3.4.2 Non-local Adverse Events

Table 95 shows the incidence of non-local AEs reported by ≥1% of all patients, including both related and unrelated events. There were 14 of these AEs. With the exception of the individual AEs surgical intervention, BCC, and upper respiratory tract infection, the incidence of each event was ≤5%. Surgical intervention and upper respiratory tract infection are fairly common events in geriatric populations. By definition, patients in these studies had at least 1 target primary nodular BCC lesion that was suitable for simple

excision surgery. However, it is not uncommon for new BCCs to occur in these patients. Overall, the frequencies of these AEs were very similar in the 2 treatment groups. This agrees with the low systemic toxicity (from clinical studies) and low bioavailability for methyl aminolevulinate (see Section 5). The remaining non-local AEs reported by ≥1% of all patients were cellulitis, localized infection, urinary tract infection, blurred vision, shortness of breath, squamous carcinoma, depression, diarrhea, headache, rhinitis, and tooth disorder.

Table 95: Non-Local Adverse Events Reported by ≥1% of All Patients in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Non-Local Adverse Event (preferred term)	Methyl aminolevulinate-PDT N = 66 n (%)	Placebo-PDT N = 65 n (%)	Total N = 131 n (%)
Any AE	38 (57.6)	28 (43.1)	66 (50.4)
Surgical intervention	10 (15.2)	9 (13.8)	19 (14.5)
Basal cell carcinoma	6 (9.1)	1 (1.5)	7 (5.3)
Upper respiratory tract infection	3 (4.5)	4 (6.2)	7 (5.3)
Cellulitis	3 (4.5)	1 (1.5)	4 (3.1)
Localized infection	2 (3.0)	1 (1.5)	3 (2.3)
Urinary tract infection	2 (3.0)	1 (1.5)	3 (2.3)
Blurred vision	2 (3.0)	1 (1.5)	3 (2.3)
Shortness of breath	1 (1.5)	1 (1.5)	2 (1.5)
Squamous carcinoma	2 (3.0)	0	2 (1.5)
Depression	1 (1.5)	1 (1.5)	2 (1.5)
Diarrhea	2 (3.0)	0	2 (1.5)
Headache	2 (3.0)	0	2 (1.5)
Rhinitis	2 (3.0)	0	2 (1.5)
Tooth disorder	0	2 (3.1)	2 (1.5)

Source: Statistical Table 2.22, BCC ISS.

The types and numbers of non-local AEs that were reported differed in the placebo-controlled studies of primary nodular BCC. Non-local AEs were experienced by 46.2% of patients in Study 307/00 and 54.5% of patients in Study 308/00.

Table 96 shows the severity and relationship to study treatment for non-local AEs reported by ≥1% of all patients. None of the non-local AEs related to study treatment were classified as severe. Only 6 patients had non-local AEs that were considered related to study treatment. In the methyl aminolevulinate cream 168 mg/g-PDT treatment group, non-local events considered related to treatment included 1 of 2 instances of blurred vision, 1 of 2 instances of headache, 1 instance of fatigue, 1 instance of lymphadenopathy, and 1 instance of nose bleeding. In the placebo group, non-local AEs considered related to treatment included 1 instance of sinus congestion and 1 instance of telangiectasia.

Table 96: Severity and Relationship to Treatment of Non-Local Adverse Events Reported by ≥1% of All Patients in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Non-Local Adverse Event (preferred term)	Methyl aminolevulinate-PDT N = 66 n (%)		Placebo-PDT N = 65 n (%)		Total N = 131 n (%)	
	Related	Not related	Related	Not related	Related	Not related
Any non-local AE						
Mild	2 (50.0)	9 (26.5)	1 (50.0)	13 (50.0)	3 (50.0)	22 (36.7)
Moderate	2 (50.0)	23 (67.6)	1 (50.0)	10 (38.5)	3 (50.0)	33 (55.0)
Severe	0	2 (5.9)	0	3 (11.5)	0	5 (8.3)
Surgical intervention						
Mild	0	2 (20.0)	0	3 (33.3)	0	5 (26.3)
Moderate	0	8 (80.0)	0	5 (55.6)	0	13 (68.4)
Severe	0	0	0	1 (11.1)	0	1 (5.3)
Basal cell carcinoma						
Mild	0	0	0	0	0	0
Moderate	0	6 (100)	0	1 (100)	0	7 (100)
Severe	0	0	0	0	0	0
Upper respiratory infection						
Mild	0	3 (100)	0	3 (75.0)	0	3 (42.9)
Moderate	0	0	0	1 (25.0)	0	4 (57.1)
Severe	0	0	0	0	0	0
Cellulitis						
Mild	0	1 (33.3)	0	0	0	1 (25.0)
Moderate	0	2 (66.7)	0	1 (100)	0	3 (75.0)
Severe	0	0	0	0	0	0
Localized infection						
Mild	0	0	0	1 (100)	0	1 (33.3)
Moderate	0	2 (100)	0	0	0	2 (66.7)
Severe	0	0	0	0	0	0
Urinary tract infection						
Mild	0	1 (50.0)	0	0	0	1 (33.3)
Moderate	0	1 (50.0)	0	1 (100)	0	2 (66.7)
Severe	0	0	0	0	0	0
Blurred vision						
Mild	1 (100)	1 (100)	0	1 (100)	1 (100)	2 (100)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 96: Severity and Relationship to Treatment of Non-Local Adverse Events Reported by ≥1% of All Patients in Placebo-Controlled Studies in Primary Nodular BCC

ITT Population

Non-Local Adverse Event (preferred term)	Methyl aminolevulinate-PDT N = 66 n (%)		Placebo-PDT N = 65 n (%)		Total N = 131 n (%)	
	Related	Not related	Related	Not related	Related	Not related
Shortness of breath						
Mild	0	1 (100)	0	0	0	1 (50.0)
Moderate	0	0	0	1 (100)	0	1 (50.0)
Severe	0	0	0	0	0	0
Squamous carcinoma						
Mild	0	0	0	0	0	0
Moderate	0	2 (100)	0	0	0	2 (100)
Severe	0	0	0	0	0	0
Depression						
Mild	0	0	0	0	0	0
Moderate	0	1 (100)	0	1 (100)	0	2 (100)
Severe	0	0	0	0	0	0
Diarrhea						
Mild	0	0	0	0	0	0
Moderate	0	2 (100)	0	0	0	2 (100)
Severe	0	0	0	0	0	0
Headache						
Mild	1 (100)	1 (100)	0	0	1 (100)	1 (100)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Rhinitis						
Mild	0	2 (100)	0	0	0	2 (100)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Tooth disorder						
Mild	0	0	0	1 (50.0)	0	1 (50.0)
Moderate	0	0	0	1 (50.0)	0	1 (50.0)
Severe	0	0	0	0	0	0

Note: The denominator is the number of patients in a treatment group who reported each AE.
Source: Statistical Table 2.22, BCC ISS.

8.3.5 Summary

- Local AEs occurred in 74% of patients treated with methyl aminolevulinate cream 168 mg/g-PDT and 46% of patients treated with placebo-PDT.
- Approximately half of the related local AEs in the methyl aminolevulinate cream 168 mg/g-PDT group were assessed as mild; in the placebo-PDT group, 70% were mild. None of the related local AEs were assessed as severe.
- As expected, methyl aminolevulinate cream 168 mg/g-PDT was associated with local phototoxic events such as burning sensation in skin, erythema, skin pain, and stinging skin. The most frequent related events reported by patients treated with methyl aminolevulinate cream 168 mg/g-PDT were burning sensation in skin (28.8%) and erythema (21.2%).
- In patients treated with methyl aminolevulinate cream 168 mg/g-PDT, all moderate local AEs had resolved. In patients treated with placebo-PDT, 1 patient had a moderate AE (sinus congestion) classified as related and local that had not resolved.
- Non-local AEs were reported in 57.6% of patients in the methyl aminolevulinate cream 168 mg/g-PDT treatment and 43.1% in the placebo-PDT treatment. By far, the majority of non-local events were considered not related to study treatment.

8.4 Active-Controlled Studies

8.4.1 Comparison to Excision Surgery in Primary Nodular BCC

This section summarizes the safety results of Study 303/99, in which methyl aminolevulinate cream 168 mg/g-PDT was compared to simple excision surgery in patients with primary nodular BCC. Methyl aminolevulinate cream 168 mg/g-PDT was administered as 2 treatments, 7 days apart. If the 3-month follow-up evaluation found that the treatment had not been successful, lesions treated with methyl aminolevulinate cream 168 mg/g-PDT could receive the same 2-session treatment a second time or they could be surgically excised. AEs were collected until 3 months after the last treatment; patients are being followed for 5 years to evaluate lesion recurrence.

- Local AEs occurred in 50% of patients treated with methyl aminolevulinate cream 168 mg/g-PDT and 16% of patients treated with surgical excision.
- Although only 16 of 49 surgery patients were reported to have received anesthetics during the study, it must be assumed that 100% of patients received local anesthesia prior to surgery. No MAL-PDT patients received anesthetics in this study.
- No patients in the MAL-PDT group reported any skin infections, whereas there were 3 patients with skin infection in the surgery group, one of which was considered related to treatment by the investigator.

- As expected, methyl aminolevulinate cream 168 mg/g-PDT was associated with local phototoxic events. The most frequently reported related local AEs in the methyl aminolevulinate cream 168 mg/g-PDT treatment group were burning sensation in skin (30.8%), erythema (13.5%), and skin pain (11.5%).

- Only 1 of the related local events in the methyl aminolevulinate cream 168 mg/g-PDT treatment group (burning sensation in skin) was assessed as severe; the majority of these AEs were assessed as mild. Almost all local events in the methyl aminolevulinate cream 168 mg/g-PDT treatment group were considered related to study treatment. All severe and moderate related local AEs in the methyl aminolevulinate cream 168 mg/g-PDT treatment group resolved. Relatively few related local events were reported in the surgery treatment group, and all were mild.

- Non-local AEs were reported with similar frequencies (13.5% versus 18.4%) in the 2 treatment groups. Two events in the methyl aminolevulinate cream 168 mg/g-PDT treatment group classified as non-local AEs (i.e., tingling skin and pricking skin sensation) were actually local reactions and considered related to study treatment. Most of the remaining non-local events were considered not related to study treatment. Thus, methyl aminolevulinate cream 168 mg/g –PDT does not produce a higher incidence of systemic AEs than surgical excision.

8.4.2 Comparison to Cryotherapy in Primary Superficial BCC

This section summarizes the safety results of Study 304/99, which compared the safety and efficacy of methyl aminolevulinate cream 168 mg/g-PDT to cryotherapy in patients with primary superficial BCC.

Lesions in the methyl aminolevulinate cream 168 mg/g-PDT treatment group were treated once with methyl aminolevulinate cream 168 mg/g-PDT. In the event of treatment failure at the 3-month follow-up visit, lesions were treated with 2 sessions of methyl aminolevulinate cream 168 mg/g-PDT, 7 days apart. Lesions in the cryotherapy group were treated with 2 freeze-thaw cycles, generating a frozen rim zone of 3 mm. If the 3-month follow-up evaluation found treatment had failed, a second cryotherapy treatment, identical to the first, was instituted. AEs were collected until 3 months after the last treatment; patients are being followed for 5 years to investigate lesion recurrence.

- Seventy-five percent of patients in the methyl aminolevulinate cream 168 mg/g-PDT treatment group experienced at least 1 AE, compared to 79% of patients in the cryotherapy treatment group. Patients in the methyl aminolevulinate-PDT group could receive up to 3 treatments; patients in the cryotherapy group received a maximum of 2 treatments.

- Local AEs occurred in 70% of patients treated with methyl aminolevulinate cream 168 mg/g-PDT and 78% of patients treated with cryotherapy.

- The most frequently reported related local AEs in the methyl aminolevulinate cream 168 mg/g-PDT treatment group were skin pain (36.7%) and crusting (35.0%), versus crusting (44.8%) and skin pain (32.8%) in the cryotherapy treatment group.

- Most of the related local AEs in the methyl aminolevulinate cream 168 mg/g-PDT group were mild. Almost all local events in both treatment groups were considered related to study treatment. With the exception of 1 case of moderate burning sensation in skin in a patient treated with cryotherapy, all moderate and severe related local events in both treatment groups were resolved at the 3-month follow-up visit.

- Non-local AEs were reported with similar frequencies in the 2 treatment groups. Non-local AEs were reported by 17 patients (28.3%) treated with methyl aminolevulinate cream 168 mg/g-PDT and 21 (36.2%) treated with cryotherapy. Some events classified as non-local, such as application site reaction and warm skin, were actually local reactions and were considered related to study treatment. Most of the remaining non-local events were considered not related to study treatment. Thus, methyl aminolevulinated cream 168 mg/g-PDT does not produce a higher incidence of systemic AEs than cryotherapy.

8.5 Studies in High-Risk BCC Unsuitable For Conventional Treatment

This section summarizes the safety results of Study 205/98 and Study 310/00 (196 patients), which investigated the safety and efficacy of methyl aminolevulinate cream 168 mg/g-PDT in high-risk superficial and nodular BCC unsuitable for conventional treatment.

One hundred fifty (77%) patients had 1 or more AEs, for a total of 522 events. Fourteen (7%) patients had a total of 18 SAEs (1 event, burning sensation in skin, was considered related to treatment), and 9 of these patients died (not related). Ten patients discontinued because of AEs, all of which were regarded as not related to treatment. Nineteen percent of patients had 1 AE; 13% had 2 AEs; 12% had 3 AEs; and 33% had 4 or more Aes. Of the 14 patients who had SAEs, only 1 was considered related to treatment. Eleven patients had 1 SAE, 2 had 2 SAEs, and 1 had 3 SAEs. A total of 138 patients (70%) experienced local AEs and 61 patients (31%) experienced non-local AEs.

- Approximately 70% of patients had at least 1 local AE. The most frequently occurring such events were burning sensation in the skin in 36.7% of patients, skin pain in 32.1%, erythema in 30.1%, stinging skin and 27.6%, and crusting in 14.8%.

- Approximately 43% of related local AEs were moderate, 40% mild, and 17% severe. All moderate and severe related local events resolved except for 6 events of moderate erythema, 5 of which were remaining at last contact with the patients and 1 of which had an unknown outcome.

- All non-local AEs occurred in less than 5% of patients. The most commonly occurring non-local AEs were surgical intervention, BCC, and headache. (BCC was reported as an AE if the patient experienced new BCC lesions other than those for which he or she enrolled in the study.) Some events classified as non-local, such as pricking skin sensation, skin warm, and eye pain, may have been local phototoxic reactions an were considered related to study treatment. Most of the remaining non-local events were considered not related to study treatment.

8.6 Clinical Assessment of Liver Function

Liver function tests, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin, were monitored in Studies 101/97, 202/98, 203/98, 204/98, and 205/98.

With regard to the 2 exploratory studies, in Study 101/98, the treatment dose varied for different lesions within the same patient and in Study 204/98 5-fluorouracil and MAL cream were administered to different lesions within the same patient. Because of the impossibility of attributing any systemic findings to a particular treatment and the small number of patients involved in these studies, the data are not presented or discussed further.

In Study 202/98, blood samples were obtained from a total of 99 patients with AK lesions, who received a single PDT treatment with cream concentrations of 80 mg/g or 160 mg/g for 1 or 3 hours before illumination. In Study 203/98, blood samples were obtained from a total of 127 patients with BCC lesions, who received a single treatment with 168mg/g cream applied for 1, 3, 5 or 18 hours before illumination. In Study 205/98, blood samples were obtained from a total of 78 patients with 'high-risk' BCC lesions, who received 2 treatment sessions with an interval of 1 week. Patients failing to show complete response after 3 months received a second treatment cycle of two sessions. The light dose and other parameters of illumination used in all three studies were identical to those subsequently used in all Phase 3 studies. Blood samples for clinical chemistry were taken 4 to 9 days after the PDT treatment in the Phase 2 studies and a similar interval after the second and fourth PDT session in the Phase 3 Study 205/98.

Local laboratories with different reference ranges for the specific laboratory parameters were used within each study. The reference ranges differ also between genders. To standardize the laboratory data between centres and gender we presented the changes from before to after PDT as the percentage of the length of the reference range. Increases or decreases of more than 40% of the reference range are commented on in the analyses below.

A typical reference range for ALT and AST in these studies was 10 – 50 U/L and for bilirubin 3 – 26 μmol/L. For these reference ranges, an increase of more than 40% of the reference range means an increase of more than 16 U/L for ALT or AST, and for bilirubin an increase of more than 9.2 μmol/L. These increases are modest, since a clinically relevant increase in these laboratory parameters is often defined as an increase of more than 2 times the upper reference limit, meaning an increase of more than 100 U/L for ALT and AST and 52 μmol/L for bilirubin.

Table 97 summarizes the changes from baseline with respect to the reference range for the 226 patients in the two Phase 2 studies 202/98 and 203/98. For ALT, the changes are randomly distributed with less than 3% showing an increase of 40%-80% and 0.4% (1 patient) greater than 80% with none reaching twice the baseline value. There is no relationship to dose in terms of concentration of cream or duration of application. The results for AST are very similar with no patient showing an increase of 80% and no

relationship to dose. The bilirubin data are likewise randomly distributed with no value increasing by as much as 100%.

Table 97: Change from Baseline – Studies 202/98 and 203/98

Laboratory test	Decrease > 80%	Decrease 40% to 80%	Decrease or Increase < 40%	Increase 40% to 80%	Increase > 80%
ALT (N=226)*	2 (0.9%)	5 (2.2%)	211 (93.3%)	6 (2.7%)	1(0.4%)
AST (N=226)*	0 (0%)	5 (2.2%)	216 (95.6%)	4 (1.8%)	0 (0%)
Bilirubin (N=226)**	0 (0%)	3 (1.3%)	215 (95.1%)	0 (0%)	1 (0.4%)

* 1 patient with missing value ** 7 patients with missing value

Table 98 shows the change from baseline with respect to the reference range for the 78 patients in Study 205/98 who received two PDT sessions. Again the data are randomly distributed with only modest changes.

Table 98: Change from Baseline in Study 205/98 Patients Who Received 2 PDT Sessions

Laboratory test	Decrease > 80%	Decrease 40% to 80%	Decrease or Increase < 40%	Increase 40% to 80%	Increase > 80%
ALT (N=78)*	2 (2.6%)	2 (2.6%)	71 (91.0%)	1 (1.3%)	0 (0%)
AST (N=78)*	0 (0%)	1 (1.3%)	73 (93.6%)	2 (2.6%)	0 (0%)
Bilirubin (N=78)**	0 (0%)	0 (0%)	68 (87.2%)	2 (2.6%)	0 (0%)

* 2 patients with missing value ** 8 patients with missing value

Table 99 shows the liver function tests in the same study after each treatment cycle of 2 sessions 3 months apart ie, 4 to 9 days after the second and fourth sessions. There is no indication of a clinically significant change in these parameters after the first or second treatment cycle and no evidence of a cumulative effect.

Table 99: Liver Function Tests in Study 205/98

Laboratory test	Number of Treatments	Decrease > 80%	Decrease 40% to 80%	Decrease or Increase < 40%	Increase 40% to 80%	Increase > 80%
	2*	1 (2.7%)	1 (2.7%)	29 (78.4%)	1 (2.7%)	0 (0%)
ALT (N=37)	4**	0 (0%)	1 (2.7%)	23 (62.2%)	1 (2.7%)	1 (2.7%)
	2*	0 (0%)	0 (0%)	31 (83.8%)	1 (2.7%)	0 (0%)
AST (N=37)	4*	0(0%)	0(0%)	25 (67.6%)	1 (2.7%)	0 (0%)
	2***	0 (0%)	0(0%)	28 (75.7%)	1 (2.7%)	0(0%)
Bilirubin (N=37)	4****	0(0%)	0(0%)	21 (56.8%)	1 (2.7%)	0 (0%)

* 5 patients with missing values ** 11 patients with missing values
*** 8 patients with missing values **** 15 patients with missing values

For ALT in the 2 Phase 2 studies, 6.6% of patients were above the normal range at baseline and 5.3% after treatment. In the 1h application group two patients had values above the normal range after PDT but both were above the normal range before PDT. In the 3h group four patients had values above the upper limit of normal after PDT but again values were above the limit before PDT in all four patients. In the 5h group three patients had values above the upper limit of normal after PDT and again all three were raised before PDT. In the 18h group three patients had values above the normal range after PDT; two were raised and one was within the normal range before PDT.

In Study 205/98 the proportion of ALT and AST values above the normal range after PDT was lower than before treatment for the whole population and in those patients with values above baseline before treatment. There was no tendency for the number transitioning to above the normal range to be higher in those receiving 2 treatment cycles than one

Conclusions

The liver function tests results recorded at baseline and after treatment in these 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.

In light of the absence of clinically relevant findings in the laboratory parameters during the phase II studies a decision was made not to perform further monitoring of laboratory parameters in phase III studies.

8.7 Compassionate Use Program (Study 001/97)

8.7.1 Patient Disposition and Demographics

The compassionate use program stopped enrolling new patients on 28 February 2002. The clinical study report for Study 001/97 summarizes the data collected from 16 September 1997 to 22 December 1999. The demographics of patients treated in this study are summarized in Table 100. A total of 1012 patients with 5232 AK or non-melanoma skin cancer lesions were treated with methyl aminolevulinate-PDT at the Norwegian Radium Hospital, Oslo. The majority of lesions were BCC (3457) and AK (1470). From November 1998 onward, all AEs were recorded on case report forms. The average age of patients treated in this program was 67.9±13.3 years.

Table 100: Demographics in the Compassionate Use Program

Indication*	Number of Patients *	Age (years)†			
	N	Mean	Std	Min	Max
Actinic keratosis	422	70.1	12.8	14	94
Basal cell carcinoma	782	67.3	13.4	22	98
SCC / Bowens	29	71.8	11.3	54	87
Mixed forms	6	71.6	13.7	54	88
Missing	146	69.8	12.0	30	92
Total	1011 ‡	67.9	13.3	14	98

*A patient could be in more than 1 diagnostic group.
† Age was not recorded for 1 patient.
‡ Total number of patients with at least 1 lesion satisfying the diagnosis.
Data source: Table 1 in the 001/97 study report, BCC ISS.

8.7.2 Extent of Exposure

Most lesions (85%) received 1 treatment, 12% 2 treatments, 2% 3 treatments, and less than 1% of the lesions received 4 or 5 treatments. Information about lesion preparation prior to treatment was collected for 81% of the lesions, of which 97% were prepared. The application time ranged from 1 hour to 33 hours, with a median of 3 hours and a mean of 3.3±2.5 hours. The light dose ranged from 25 J/cm^2 (for AK lesions only) to 100 J/cm^2 (for BCC and AK lesions), with the majority of lesions (99%) receiving 50 or 75 J/cm^2. Three light sources were used, but a broadband lamp emitting light of wavelength of 570 to 670 nm was used in most cases (97%). The other light sources used were a 420-nm lamp and a 630-nm laser.

8.7.3 Adverse Events

8.7.3.1 Local Adverse Events

The questionnaire for pain was completed by 43% of the patients, of whom 45% reported pain (Table 101). The questionnaire regarding erythema was completed by 37% of the patients, of whom 84% reported erythema. There were no differences in pain or erythema between the types of lesions.

Table 101: Local Adverse Events in the Compassionate Use Program

Diagnosis	Number of Patients*	Number of Patients Evaluable for Pain			Number of Patients Evaluable for Erythema		
		n	Pain reported		n	Erythema reported	
			n	%		n	%
BCC	782	336	142	42	287	231	81
AK	423	157	72	46	136	116	85
Others	29	11	6	55	9	7	78
Mixed form	6	5	2	40	4	3	75
Missing	146	37	14	38	29	23	79
Total	1012	436	197	45	375	315	84

* The numbers of patients given are those with at least 1 lesion satisfying the diagnosis, i.e., 1 patient may be in more than 1 diagnostic group but the total is the actual number of patients. The percentage is calculated from the number of patients who had a value registered (yes or no) for pain or erythema.
Data source: Table 7 in the 001/97 study report, BCC ISS.

8.7.3.2 Non-Local Adverse Events

Just 3 non-local AEs were reported: dizziness, hair loss, and blurred vision (Statistical Listing 1 in the Study 001/97 report). One patient reported dizziness as a non-serious AE that lasted 15 minutes. No action was taken and the event resolved. No information was given about relationship to study treatment or about severity. Another patient reported hair loss 3 to 10 cm away from treatment site, which started 1 week after treatment. It was of moderate severity and of uncertain relationship to methyl aminolevulinate-PDT; the event did not resolve. A third patient reported light sensitivity and blurred vision for distant objects. The treatment site was 3 cm above the eyebrow. The event was severe and of uncertain relationship to study treatment; the event resolved.

8.7.4 Serious or Other Significant Adverse Events

No deaths, SAEs, or other significant AEs were reported. No patients discontinued due to AEs.

8.8 Postmarketing Data

8.8.1 Introduction

The aim of this post-marketing safety data section is to present a global overview of the post-marketing experience collected by PhotoCure from the countries where methyl aminolevulinate cream is marketed. The post-marketing experience is a summary of the data submitted as Periodic Safety Update Reports to regulatory authorities in all countries having approved the product, as required by ICH guideline E2C.

The post-marketing experience dates from the International Birth Date as defined by the ICH guidelines, ie, the date when the product was first granted marketing authorization in any country. For MAL-PDT, this date is 15 June 2001. The period reviewed here extends from this date to 14 June 2003, corresponding to a 24-month survey.

8.8.2 Worldwide Market Authorization Status

Methyl aminolevulinate cream was approved for marketing in Sweden as the first country on 15 June 2001, for treatment of actinic keratoses and basal cell carcinoma. Methyl aminolevulinate cream is currently approved for treatment of AK and/or BCC in 17 countries world wide, see Regulatory Status below for details (Section 10). No marketing authorization has been rejected for safety reasons, and there have been no marketing authorization suspensions or restrictions on distribution.

8.8.3 Patient Exposure

In the 24 months period, 11, 693 tubes of cream have been sold world-wide. Based on clinical experience, one tube is used for about 3 patients, thus, approximately 35,079 patients have been exposed in routine clinical use. In addition, 1337 tubes of cream have been sold for named patient use, and this number approximates the number of patients exposed in named patient use.

8.8.4 Demographics of ADR Reports

There have been 8 patients with post-marketing ADRs, i.e. routine clinical use and named-patient use that were unexpected, or serious and expected. There were 2 male and 5 female patients, and in addition one patient with both gender and age unknown. The ages are between 30 and 86 years old (one female patient had unknown age, and one patient had both unknow age and gender). In addition, 5 patients had non-serious and expected adverse events reported by a health professional. Of these, there were 2 females, one male and 2 of unknown gender.

8.8.5 ADR Reports

The ICH E2C guideline requires periodic reporting to regulatory authorities of:

- Serious reactions, and non-serious unlisted reactions, from spontaneous notifications;
- Serious reactions reported from studies;
- Serious and non-serious unlisted reactions found in the literature; and
- Serious reactions reported from regulatory authorities

('Listed' in this context refers to Product Safety Information. Listed reactions are expected reactions, while unlisted reactions are unexpected.)

All information about ADRs in clinical studies is found in the Safety section of this Briefing document. Therefore only data from commercial use of MAL-PDT is summarized here.

During the 24 months period, the following serious and non-serious unexpected, serious and expected, and non-serious and expected ADR cases have been reported from routine clinical use and named-patient use, all spontaneously reported by health care professionals:

8.8.5.1 Serious and non-serious unexpected cases

Infections and Infestations: 1 herpes zoster.

NO-GD-0310606: This health care professional case involves a 86-year-old female patient treated with MAL-PDT for actinic keratosis. One week later, **herpes zoster** was discovered in the treated area.
Company evaluation: Conditional. The mechanism of reactivation of Varicella - zoster virus is unknown. However, contribution of the photodynamic therapy cannot be excluded as lesions appeared on the treated areas.

Nervous System Disorders: 1 dizziness and 1 headache.

NO-GD-0310603: This health care professional case involves a female patient who received a PDT cycle for a superficial basal cell carcinoma (2x2 cm) on the chest. After both PDT sessions, the patient got **dizzy** and experienced a general feeling of discomfort (reaction onset after illumination). The patient was observed for about one hour after illumination.
Company evaluation: Possible. Due to suggestive rechallenge, causal role of MAL-PDT cannot be excluded.

SE-GD-0310605: This health care professional case involves a 60-year-old female patient treated with MAL-PDT for actinic keratosis on the forehead. After treatment, the patient experienced **severe headache**. There were remaining symptoms one month later. In this period the patient also experienced three migraine-like episodes.
Company evaluation: Conditional. Medical history of patient was not provided and headaches may have numerous causes. However, due to suggestive time to onset, causal role of MAL-PDT cannot be excluded.

Skin and Subcutaneous Tissue Disorders: 2 eczemas.

DE-GD-0310424: A dermatologist with experience in PDT and in the use of MAL cream reported his first adverse event with MAL. After the first treatment the patient (gender and age not specified) developed severe local reddening, erythema and **eczema** in the treated area (face). The doctor suspects that MAL cream has caused an allergic reaction. The patient started an anti-allergic treatment.
Company evaluation: Possible. Due to suggestive time to onset and area of reaction, hypersensitivity to the product cannot be excluded.

DK-GD-0310607: This health care professional case involves a 30-year-old female patient who presented with presented with **acute eczema** and itch and hyperreactivity of the untreated skin after several treatment with MAL-PDT for necrobiosis lipoidica on the lower legs. It was described as a severe generalised itch and scaly dryness. Hypersensitivity test performed by the dermatologist revealed sensitivity to ALA and MAL cream.
Company evaluation: Possible. Hypersensitivity to the product was assessed by the dermatologist.

8.8.5.2 Serious and expected cases

Two facial edemas. Both **treatments** (same lamp, Aktilite CL 128) were performed on the same day by the same dermatologist.

DE-GD-0310425: A 66-year-old male patient experienced a severe pain during the first treatment of an actinic keratosis (AK) on the head. Illumination had to be interrupted after approximately 9 minutes (the pre-selected illumination time of the lamp was 11:56 minutes). In the following minutes, the patient developed a serious erythema and **edema in the face**. The patient was hospitalised and treated with tramadol and diazepam. The next day he had recovered and discharged.

DE-GD-0310426: A 78-year-old male patient developed severe pain during a the first PDT treatment of an AK on the head. Nevertheless, the pre-selected illumination time of the lamp was 11:56 minutes and the patient was treated for the complete time. The patient was sent home. The next day the patient came back to hospital. He needed assistance (from his GP) due to a serious erythema and **edema of the face.** Eyelids were particularly swollen. The dermatologist asked for support of an ophthalmologist. The patient was discharged from hospital with a corrective treatment (not specified). The dermatologist assessed the case as serious.
Company evaluation of both cases: Possible. Phototoxic reactions are expected during photodynamic therapy. It is unknown whether the patient was on any other medication or

had any history of photosensitivity. However due to temporal relationship, a causal role of MAL cannot be excluded.

SE-GD-0210283: A 66-year-old female patient treated with MAL-PDT for Bowen's disease. During light exposure, the patient experienced intense pain. A Waldman lamp with intensity 250mW/cm^2 (70J/cm^2) was used. This lamp is not the same as the Curelight lamp. The patient was illuminated for 4 minutes and 40 seconds. Vesicles in an area of 10x20 cm from the neck to the breast on the left side appeared during the following evening, indicating **second-degree burn**. The patient experienced fever, pain and difficulties to move. The patient was away from work and unable to perform normal activities during one month following this incident. Reporter evaluation: not available. Company evaluation: Possible. The case was considered serious as the patient could not perform normal activities during one month following the incident, representing a significant disability. This ADR was listed as a local phototoxic reaction (vesicles and edema) because phototoxic reactions can resemble a second-degree burn. The Sponsor feels that the light intensity used was rather high and could possibly have produced thermal changes in the patient's skin. The ADR resolved. (Case included in the ISS).

8.8.5.3 Non-serious and expected cases

One patient (MET02030001-00) in Sweden had a lesion on her eyebrow. After cream application, but prior to illumination, she experienced burning sensation while out in the sunshine. Burning sensation in skin is an expected ADR during PDT. Information on the outcome of this ADR is not available. (Case included in ISS).

One patient (MET02050002-00) in Norway had edema, erythema, and multiple vesicles, 3-5 mm in diameter, in the area that had been treated with methyl aminolevulinate cream 168 mg/g-PDT. These ADRs resolved. (Case included in ISS)

One patient (SE-GD-0210284) in Sweden, age and gender unknown, had intense pain, erythema and some numbness on the cheek the day after MAL-PDT for a basalioma on the lip. Duration was 2 months. The patient recovered.

One patient (NZ-GD-0210162) in New Zealand, a 45-year-old female, had hypopigmentation evident after crust had peeled, excessive blistering well beyond the margins of the tumor, and crusting. The cream spread beyond the lesion, whilst under occlusion. The patient recovered.

One patient (DK-GD-0310604) in Denmark, a 51-year-old male patient with AK, experienced redness and pain spreading outside the area of MAL cream application on the forehead. It occurred before illumination and lasted 4 days. The patient recovered.

8.8.6 Conclusion – Post-marketing

During the 24-month period since the first marketing authorization was granted for methyl aminolevulinate cream, 15 June 2001 to 14 June 2003, there have been only a very few serious ADR reports. There is no indication of a change in safety profile as compared to what was known at the time of filing NDA 21-576.

9 REGULATORY STATUS

Methyl aminolevulinate cream was approved for marketing in Sweden as the first country on 15 June 2001, for treatment of actinic keratoses and basal cell carcinoma. Methyl aminolevulinate cream is currently approved for treatment of AK and/or BCC in 17 countries worldwide.

The table below shows the countries having approved the product and the date of approval. All listed European countries and New Zealand have approved the product 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 actinic keratoses on the face and scalp when other registered therapies are unacceptable and for primary treatment of superficial and/or nodular basal cell carcinoma where surgery is considered inappropriate.

Table 102: Regulatory Status of MAL Cream

Country	Date of Approval
Australia	04 Apr 2003
Austria	11 Sep 2002
Belgium	07 Oct 2002
Denmark	21 Mar 2002
Finland	29 Apr 2002
Germany	31 Jan 2002
Greece	22 Apr 2002
Iceland	01 Mar 2002
Ireland	22 Mar 2002
Italy	27 Nov 2001*
Luxemburg	13 Mar 2002
Malta	09 Nov 2002
New Zealand	07 Feb 2002
Norway	17 Jan 2002
Spain	06 Aug 2002
Sweden	15 Jun 2001
United Kingdom	08 Apr 2002
* Italy has recognized the European approval; national approval is not yet issued.	

10 BENEFIT AND RISK – ROLE OF MAL PDT TREATMENT

The clinical development program for MAL-PDT was designed to fulfill the current 3 main treatment goals in BCC, complete eradication of the cancer, preservation or restoration of normal function, and cosmesis.[20] In addition, to assure that this criteria could be applicable to BCC in general, the clinical development program contained patients with specific lesion characteristics. Therefore, separate study protocols were designed to assess the efficacy and safety of MAL-PDT in two main BCC populations; patients with BCC that due to location and/or size had higher risk for recurrence (so called high risk BCC; BCC unsuitable for other treatments) and patients with BCC that due to location and/or size had lower risk for recurrence (so called low-risk BCC; primary BCC). In both study populations 2 histological types of BCC were included, nodular and superficial BCC. This distinction was based on recommendations from experts in the field as well as published literature in management of BCC.[20] This distinction is also justified because within each risk group, different treatment options should be used.[15,20] For example, in the low-risk BCC population electrodessication with curettage and cryotherapy are two non-surgical treatment options that are recommended. However, throughout the clinical development infiltrating and morpheaform BCC have been excluded. Thus, based on well-accepted criteria the clinical documentation of MAL-PDT has been obtained in patients with both nodular and superficial lesions in both high-risk BCC and low-risk BCC populations.

The pharmacokinetic and concentration-response studies established that a PDT session with a regimen of MAL 168 mg/g cream applied for 3 hours is more effective than a lower concentration or a shorter application time. Phototoxic reactions are frequent with all optimally effective cream strengths tested and longer application times are less convenient and may cause more local AEs, and less well localized phototoxicity. Illumination with non-coherent light of wavelength 570-670 nm with a total energy of 75 J/cm^2 is adequate to achieve photoactivation with complete photobleaching, which is desirable in principle and avoids the risk of persistent photosensitivity.

Using the selected treatment regimen as one or two treatment cycles of two PDT sessions, response rates 3 months after the last treatment of high-risk and low-risk BCC lesions are very satisfactory and cosmetic results are excellent and superior to both excision surgery and cryotherapy. In contrast to traditional treatments, re-treatment with MAL-PDT is not associated with any worsening of the safety profile or cosmetic outcome. Histological examination of treatment site shows that there is a normal regeneration of the skin and its attributes. Also, as shown in the histological examination of treatment failures, there is no indication that the treatment has lead to change in the morphology of the cancer or that cancer cells will be trapped in scar tissue. This indicates that MAL-PDT does not exclude the successful use of other modalities in case of treatment failures.

Recurrence rates are currently available for 12 and 24 months for three of the studies. In two of these studies, where MAL-PDT was compared to surgery and cryotherapy, the results showed that the 12 and 24 months recurrence rates of MAL-PDT are lower

compared to cryotherapy and slightly higher than surgery. The recurrence rate for cryotherapy was higher than what is reported in the literature. These two studies are the only prospective, randomized and comparative studies conducted to compared recurrence rates between methods available for the treatment of BCC. A large meta analysis of 298 studies has been conducted to establish the recommended treatment for BCC[21], of which only 18 studies met the requirements. This analysis concluded that because of lack of conformity in the method of reporting no evidence-based guidelines could be developed. Since the studies included in the meta-analysis were not randomized for practical reasons, the results may be affected by selection bias. The patient populations studied in the different studies with MAL-PDT are standardized for each study. Since the recurrence rates for BCC vary depending on the location, size and histologic type of the tumor[15], and the published literature is mainly based on retrospective studies where the patient population is not standardized, it is likely that the studies examining the recurrence rates of surgery and cryotherapy mainly include patients with low-risk tumors.[20]

In preclinical toxicology studies, intravenous administration of high doses of MAL in rat for long time (14 days) identified the liver as potential target organ. However, in local tolerance studies with MAL-PDT including repeated treatments, prolonged application time, and large areas of cream application in rats and minipigs, no hepatotoxicty or other systemic toxicity was observed. More importantly, liver enzymes were examined in clinical studies, no signs of hepatotoxicity from MAL-PDT was observed. This is in accordance with the low systemic availability of the active substance shown in cadaver skin models using radiolabeled substance.

Despite a high incidence of expected and transient local adverse events associated with phototoxicity, the treatment is generally well tolerated with withdrawals rarely attributable to adverse events. In addition, frequency and severity of local adverse events were similar to cryotherapy. Similar to placebo-PDT, excision surgery, and cryotherapy MAL-PDT has been shown to be very safe with no evidence of treatment-attributable systemic (non-local) adverse events.

In healthy volunteers MAL cream was shown to be a potential irritant and skin sensitizer after 4 days of application. This was observed during 3 weeks of continuous exposure in provocative skin sensitization study. In the clinical use, only 3 hours application of MAL cream should be used followed by light illumination. During 3 hours application of cream no skin irritation has been observed in acute skin irritation study. It is known that skin sensitization may be correlated with degree of skin irritation. Furthermore, MAL 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 MAL has been spontaneously reported. In controlled clinical studies in over 900 patients none of the AE reported was suspected to reflect contact sensitization. Therefore, sensitization does not seem to be a clinically significant problem and is only observed under extreme conditions. Cross-sensitization to endogenous ALA was also examined, and no cross-sensitization was observed. In regard to health care providers that apply the cream on the lesion sites, they are recommended to use medical gloves to protect against direct skin contact with the cream. The sponsor has performed penetration studies of gloves to be able to provide guidance to the health care personnel.

MAL-PDT is convenient and very acceptable to patients, and due to its high tumor selectivity it results in superior tissue preservation relative to that of surgery or cryotherapy. Several lesions may be treated concurrently. There is no requirement to avoid light exposure after treatment. The consistent response rates obtained across study populations and across 6 multicenter studies, indicate that MAL-PDT is less operator-dependent than other forms of therapy for BCC lesions. It is known that the proper management of BCC depends on the physician's knowledge, skill and experience.[20,21] It is also possible that this difference may be one of the reasons for the variation in published sustained response rates.[21]

Partial responses have not been presented as they have been regarded as treatment failures. However, it should be recognized that a partial response may be of real value in a high-risk BCC patient as this may limit the extent of surgery required (Figure 22).

Figure 22: Partial Response in Large High-Risk BCC Lesion Following Treatment with MAL-PDT

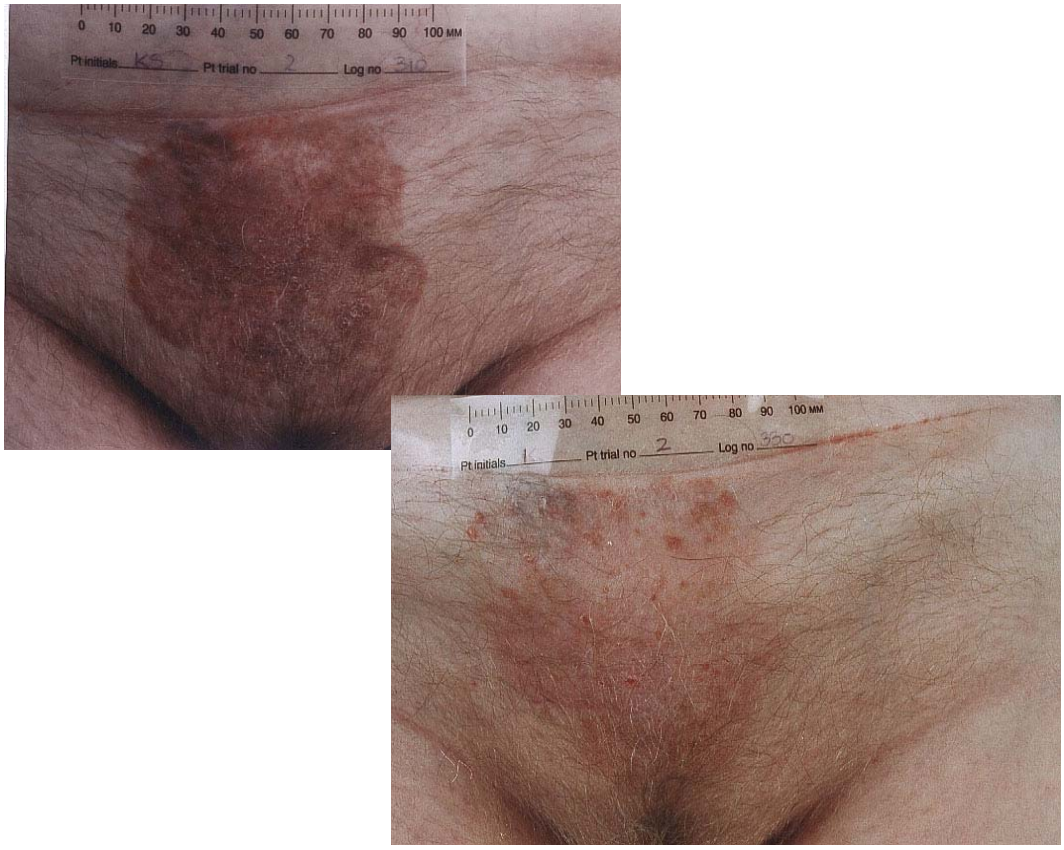


Figure 22: Study 205/98, Patient 0302, female age 69, Superficial lesion, 110 mm
Partial response, re-treated after 3 months. Non-complete response/partial response at 6 months.

Finally, unlike traditional therapies such as surgery and radiotherapy, previous treatment with MAL-PDT does not interfere with the subsequent use of repeat treatment with MAL-PDT or other treatment modalities.

11 CONCLUSIONS

Photodynamic therapy using MAL 168 mg/g Cream applied for 3 h before illumination with non-coherent light with a total fluence of 75 J/cm^2 is an effective treatment for nodular and superficial basal cell carcinoma. Especially, clear evidence for its efficacy and safety, as well as benefit over surgery and cryotherapy in low-risk superficial and nodular BCC has been provided through 4 controlled studies plus supportive studies in high-risk BCC lesions.

Response rates and recurrence rates for low-risk (primary) lesions are similar to those with excision surgery and cryotherapy. Response rates are not related to the size of the lesion or its location or to patient age, sex or skin type. Satisfactory response and recurrence rates are also obtained in lesions of a 'high-risk' category not suitable for conventional therapy and in patients at high risk of morbidity from surgery.

A treatment cycle of two sessions with an interval of one week is recommended. Response rates on re-treatment of nodular lesions failing to show a complete response after 3 months are somewhat lower than to the first treatment. However, it is clearly worthwhile to retreat nodular as well as superficial lesions when required since more than 50% of lesions show a complete response on re-treatment.

For both nodular and superficial lesions, the proportion of patients and lesions with Excellent / Good ratings of cosmetic outcome by investigators and patients are consistently high and superior to those of surgery or cryotherapy respectively. The cosmetic results in patients with high-risk lesions unsuitable for conventional therapy, many of which are located on the face and ears were also highly satisfactory. The high rates of Excellent / Good cosmetic outcome are attributable to tissue conservation with MAL-PDT. This avoids disfigurement and interference with function of vital structures which are commonly associated with surgery, particularly in the mid-face.

Despite the frequency of local phototoxic reactions, treatment with methyl aminolevulinate-PDT was very well tolerated. This is evident from the very low incidence of premature discontinuations, including studies in which patients received a second session of treatment 1 week after the first.

The profile of non-local AEs and the very low incidence of SAEs support the conclusion that methyl aminolevulinate cream 168 mg/g-PDT is devoid of systemic adverse effects and poses no safety concern.

12 REFERENCES

1. Fritsch C, Ruzicka T, editors. Fluorescence diagnosis and photodynamic therapy of skin diseases. Vienna: Springer-Verlag; 2003.
2. TL Diepgen and V Mahler. The epidemology of skin cancer. BJD. 2002, 146 (suppl. 61): 1-6.
3. Miller DL, Weinstock MA. Nonmelanoma skin cancer in the United States: incidence. J Am Acad Dermatol. 1994;30:774-778.
4. Goldberg LH. Basal cell carcinoma. Lancet. 1996;347:663-67.
5. Thissen MR, Neumann HA, Berretty PJ, Ideler AH. The treatment of basal cell carcinoma patients by dermatologists in the Netherlands. Ned Tijdschr Geneesakd 1998, 142:1563-1567.
6. Ko CB. Waiton S, Keczkes K, Bury HP. The emerging epidemic of skin cancer. Br J Dermatol. 1994;130:269-272.
7. Kopf AW. Computer analsysis of 3531 basal-cell carcinomas of the skin. J Dermatol. 1979;6:267-281.
8. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63(1-3):8-18.
9. Pennello G, Devesa S, Gail M. Association of surface ultraviolet B radiation levels with melanoma and nonmelanoma skin cancer in United States blacks. Cancer Epidermiol Biomarkers Prev 2000; 9: 291-7.
10. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales 1988-98. Br J Dermatol 2000;143: 1224-9.
11. Leong GK, Stone JL, Farmer ER, Scotto J, Reizner GT, Burnett TS, Elpern DJ. Non-melanoma skin cancer in Japanese residents of Kauai, Hawaii. JAAD 1987; 17:23-28.
12. Rahbari H, Mehregan AH. Basal cell epitheliomas in usual and unusual sites. J Cut Path 1979;6:425-431.
13. Bastiaens MT, Hoefnagel JJ, Bruijn JA et al. Differences in age, site distribution and sex between nodular and superficial basal cell carcinomas indicate different types of tumors. J Invest Dermatol 1998, 110:880-884.
14. McCormack CJ, Kelly J, Dorevitch AP. Differences in age and body site distribution of the histological subtypes of basal cell carcinoma. Arch Dermatol 1997;133:593-596.
15. Preston DS, Stern RS. Nonmelanoma cancers of the skin. New Eng J Med 1992;327:1649-1662.
16. Randle HW. Basal cell carcinoma. Identification and treatment of the high risk patient. Dermatol Surg 1996;22:255-261.

17. Telfer NR, Colver GB, Bowers PW. Guidelines for the management of basal cell carcinoma. Br J Dermatol 1999;141:415-423.

18. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Recurrent non-melanoma skin cancer in southern Australia. Int J Dermatol 1996;35(6):410-412.

19. Czarnecki D, Mar A, Staples M, Giles G, Meeham C. The development of non-melanocytic skin cancers in people with a history of skin cancer. Dermatology 1994;189(4):364-367.

20. Martinez J-C, Otley CC. The management of melanoma and nonmelanoma skin cancer: a review for the primary care physician. Mayo Clin Proc 2001 December;76:1253-1260.

21. Thissen MRTM, Neumann MHA, Schouten LJ. A systemaic review of treatment modalities for primary basal cell carcinomas. Arch. Dermatol. 1999;35:1177-1183

22. Rowe DE, Carroll RJ, Day CL. Long-term recurrence rates in reviously untreated (primary) basal cell carcinoma: Implications for patient follow-up. J Dermatol. Surg. Oncol. 1989;15 (3 March):315-328.

23. Drake LA, Ceilley RI, Cornelison RL et al. Guidelines of care of basal cell carcinoma. The American Academy of Dermatology. J Am Acad dermatol. 1992;26(1):117-120.

24. National Cancer Institute (NCI) – Skin Cancer (PDQ®: Treatment (For Health Professionals).Available from URL: http://www.cancer.gov/cancerinfo/pdq/treatment/skin/Health Professional#15

25. British Association of Dermatologists. URL: http://www.bad.org.uk/ (accessed 07-31-2003).

26. Kuijpers DIM, Thissen MRTM, Neumann MHA. Basal Cell Carcinoma, treatment options and prognosis, a scientific approach to a common malignancy. Am J Clin Dermatol 2002;3:247-259.

27. Rowe DE, Carroll RJ, Day CL. Mohs surgery is the treatment of choice for recurrent (previously treated) basal cell carcinoma. J Dermatol Surg Oncol 1989;15:424-431.

28. Goldberg LH. Basal cell carcinoma. Lancet 1996;347:663-67.

29. Kopf AW. Computer analysis of 3531 basal-cell carcinomas of the skin. J Dermatol 1979;6:267-281.

30. Swanson NA. Mohs surgery. Arch Dermatol 1983, 119:761-773.

31. Peng Q, Moan J, Warloe T, et al. Build-up of esterified aminolevulinic-acid-derivative-induced porphyrin fluorescence in normal mouse skin. J Photochem Photobiol B 1996;34:95-96.

32. Peng Q, Berg K, Moan J, Kongshaug M, Nesland JM. 5-aminolevulinic acid-based photodynamic therapy: principles and experimental research. Photochem Photobiol 1997;65:235-251.

33. Fritsch CB, Homey W, Stahl PL, Lehmann P, Ruzicka T, Sies H. Preferential relative porphyrin enrichment in solar keratoses upon topical application of aminolevulinic acid methyl ester. Photochem Photobiol 1998;68:218-221.

34. Martin A, Tope WD, Grevelink JM, et al. Lack of selectivity of protoporhyrin IX fluorescence for basal cell carcinoma after topical application of 5–aminolevulinic acid: implications for photodynamic treatment. Arch Dermatol Res.1995;287:665-674.

35. Uehlinger P, Zellweger M, Wagnieres G, Juillerat-Jeanneret L, van der Bergh H, Lange N. 5-Aminolevulinic acid and its derivatives: physical chemical properties and protoporphyrin IX formation in cultured cells. J Photochem. Photobiol B 2000;54:72-80.

36. Gederaas OA, Holroyd A, Brown SB, Vernon D, Moan J, Berg K. 5-aminolaevulinic acid methyl ester transport on amino acid carriers in a human colon adenocarcinoma cell line. Photochem Photobiol 2001;73:164-169.

37. Rud E, Gederaas O, Høgstet A, Berg K. 5-aminolaevulinic acid, but not 5-aminolaevulinic acid esters, are transported into adenocarcinoma cells by system BETA transporters. Photochem Photobiol. 2000;71:640-647.

38. Noodt BB, Berg K, Stokke T, Peng Q, Nesland JM. Apoptosis and necrosis induced with light and 5-aminolevulinic acid-derived protoporphyrin IX. Br J Cancer 1996;74:22-29.

39. Miller SJ. Biology of Basal Cell Carcinoma (Part I). J Am Acad Dermatol 1991;24:1-13.

40. Ngyen AV, Whitaker DC, Frodel J. Differentiation of Basal Cell Carcinoma. Facial Skin Malignancy. 1993;26:37-56.

41. Phillips L, Steinberg M, Maibach HI, Akers WA. A comparison of rabbit and human skin response to certain irritants. Toxicol Applied Pharmacol. 1972;21:369-382.

42. Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products, Dec. 1999.

43. Chuang TY, Popescu A, Su WP, Chute CG. Basal cell carcinoma: a population based incidence study in Rochester Minnesota. J Am Acad Dermatol 1990,22:413-417.

44. Soler AM, Warloe T, Berner A, Giercksky KE. A follow-up study of recurrence and cosmesis in completely responding superficial and nodular basal cell carcinomas treated with methyl amionlevulinate-based photodynamic therapy alone and with prior curettage. Br J Dermatol 2001;145:467-471.