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Executive Summary
NDA 21-576
September 10, 2003 Advisory Committee

Basal cell carcinoma (BCC) is one of the most common forms of skin cancer worldwide. In the United States, almost a million people per year are diagnosed with BCC. Excisional techniques (including Mohs' micrographic surgery) are commonly used for treatment of BCC and allow for histopathological confirmation of diagnosis and evaluation of tumor involvement at the margins of excision.

This New Drug Application (NDA) is for the use of methyl aminolevulinate hydrochloride cream 168 mg/g (MAL) with CureLight BroadBand Model CureLight 01 lamp (emitting red light at 570 to 670 nm) for the photodynamic therapy (MAL-PDT) treatment of primary nodular and superficial basal cell carcinoma. Approval for primary superficial BCC is contingent, in part, on a demonstration of safety and efficacy for primary nodular BCC. The application included study reports describing two vehicle controlled pivotal studies with 33 patients in each study randomized to MAL who were followed for 6 months after treatment and several open label studies in which some patients were followed for up to 2 years after treatment (see Appendix 1). The dermal safety testing of this drug product included evaluation for contact hypersensitivity. Significant issues for discussion by the Advisory Committee include:

A) Adequacy of Evidence for Effectiveness

PhotoCure demonstrated that MAL plus red light (MAL-PDT) is superior to vehicle plus red light (VEH-PDT) in the treatment of nodular BCC in two pivotal studies (Studies 307 and 308). Although the primary outcome rates achieved after up to 4 treatments (2 treatment cycles) with MAL-PDT and VEH-PDT were 76% and 34% for study 307 and 67% and 18% for study 308 respectively, (as per Sponsor's analysis) two centers drove the results in study 307 (see also FDA Biostatistical analysis – Appendix 2). The study design for 307 and 308 was complex and relied on several decision points (see Appendix 3). The primary endpoint relied on histological evaluation at 6 months post treatment, i.e. bread-loafing of specimen into sections not more than 3 mm thick. At least 6 to more than 20 sections were examined for each case, depending on the size of the lesion.

Lesion preparation may be a source of several significant concerns. The high primary outcome rates achieved by the VEH-PDT arms in the two studies may be due to lesion preparation (i.e., curettage). Differences in lesion preparation from investigator to investigator may account for very high inter-center variability (see Biostatistical analysis – Appendix 2). Differences in lesion preparation may have been difficult to avoid with the limited written instructions given to the trial investigators regarding such preparation.

It was not possible to obtain recurrence data beyond 6 months after treatment from these pivotal studies due to excision of the treatment site for histological evaluation. Instead, recurrence was evaluated in separate open-label studies. Fifty-two (52) subjects with nodular BCC were followed for up to 24 months in Study 303, an open-label multicenter trial conducted in Europe. These patients were compared to 49 subjects

treated with surgical excision using 1 to 5 mm margins. [It was unclear if surgical margins were evaluated in the excised specimens.] Follow-up data at 12 and 24 months were evaluated for recurrence. It was difficult to determine if follow-up determinations were accurate for this study because the body charts showing tumor location were not submitted. However, intent-to-treat (ITT) analysis showed that 85% of the subjects receiving surgery had no clinical recurrence by month 24 and only 67% of the subjects receiving MAL-PDT had no clinical recurrence by month 24. No histological determination for lack of recurrence was made. Twice as many subjects receiving MAL-PDT were lost to follow-up as compared to those receiving surgery.

Study 205 was a single-arm, open-label, Phase 2 study that evaluated both superficial and nodular BCC (overall BCC) for up to 24 months for recurrence (94 patients were enrolled with 52 patients having a nodular BCC component). Body charts were available for this study. Individual lesions were analyzed for recurrence rather than by patient. At month 6, the overall lesion clinical recurrence rate was 5%. None of the lesions with a nodular component showed clinical recurrence; however, superficial BCC treated with MAL-PDT had a recurrence rate of 10% at month 6, and lesions on the trunk/neck had an 18% recurrence rate. At month 12, the overall lesion recurrence rate was 9% with a notable 32% recurrence rate for lesions located on the trunk or neck. At month 24 of this study, the patient mean recurrence rate was 16% (95% confidence interval of 6 to 26%). The clinical recurrence rate was higher (21%) for superficial lesions treated with MAL-PDT than for nodular lesions (11%). Overall, lesions treated with one PDT cycle (2 treatments) had a 13% clinical recurrence rate, while lesions needing 2 PDT cycles (4 treatments) had an 18% recurrence rate by month 24. Overall, lesions located on trunk/neck had higher clinical recurrence rates (36%) than lesions located on face/scalp (9%). There was a positive correlation between lesion diameter and recurrence rates (0 to 15 mm = 3%, 16 to 30 mm = 14%, and >30 mm = 32%). Five year post-treatment recurrence data is still pending from this study which began in 1999.

B) Point Estimates of Efficacy and Comparison with Currently Available Therapy

The following issues are relevant to evaluating the validity of the point estimates for primary outcome in the MAL-PDT arm of studies 307 and 308:

1) high variability from study site to study site, which may be due in part to variable lesion preparation and limited written description of lesion preparation instructions
2) the post-treatment excision breadloafing used may miss microscopic nests of basal cell carcinoma
3) the sensitivity of the histological examination of post-treatment excision at 6 months to provide an adequate estimate of long-term recurrence rates.

Drs. Rowe, Carroll, and Day published in the March 1989 issue of the Journal of Dermatologic Surgery and Oncology, a meta-analysis review (Appendix 5) of 106 independent reports on recurrence rates for treatment of primary basal cell carcinomas using surgical excision, radiotherapy, cryosurgery, curettage and electrodessication (ED&C), and Mohs micrographic surgery. The data for this paper mixed results from lesions of varying size and location, combining results from different observers. This paper amassed data on a combined total of nearly 40,000 lesions. In this paper, the observed five-year clinical lesion recurrence rates for BCC by treatment modality were

reported as follows: surgical excision 10.1%, radiotherapy 8.7%, cryosurgery 7.5%, ED&C 7.7%, Mohs surgery 1.0%. The authors also stated the following: "A good rule of thumb is that the 10-year recurrence rate is double, or 2 times, that of the 2-year recurrence rate." This paper provides a rationale for the need for long-term follow-up for basal cell carcinoma.

C) Contact Hypersensitivity to Drug Product

Contact hypersensitivity to drug product was demonstrated in 2 provocative sensitization studies. In the first study, a provocative cumulative irritancy and sensitization (allergenicity) study was conducted in 25 healthy adult subjects randomized and tested with MAL and with vehicle cream. The first phase was stopped by the investigator after 9 days rather than the usual 21 days because of the severity of adverse skin reactions. After 9 days, 17 of the 25 subjects had contact dermatitis. Five out of 25 had reactions consistent with topical sensitization (allergic reaction).

In the second study (Appendix 4), 156 subjects were included. [Due to frequent skin reactions during induction, the investigator and PhotoCure decided not to include more subjects]. Fifty-eight of the 156 subjects decided not to participate in the challenge (allergic reaction) phase of the study. Fifty-eight of the 98 subjects proceeding to the challenge phase allowed both MAL and aminolevulinic acid (ALA, an endogenous protoporphyrin) to be tested. Forty subjects allowed only ALA to be applied due to reactions with MAL during the initial phase. PhotoCure's analysis of the sensitization potential by MAL revealed that 52% of the 58 subjects were regarded as positive with respect to contact sensitization. Only 2% of the 98 subjects demonstrated contact sensitization to vehicle. The Applicant concluded that the sensitization and irritation are related to the drug substance and not to the vehicle.

In conclusion, PhotoCure's application for methyl aminolevulinate hydrochloride cream, 168 mg/g, demonstrated a statistically significant advantage of the product over the vehicle when used in conjunction with lesion preparation (curettage) and the CureLight BroadBand Model CureLight 01 lamp (emitting red light at 570 to 670 nm) for the prespecified primary outcome measure in the photodynamic therapy (PDT) of nodular and superficial basal cell carcinoma (BCC). The committee is asked to consider the adequacy of the evidence for efficacy and recurrence of BCC, the relative efficacy/non-recurrence as compared to existing therapies, and the potential for and consequences of sensitization of patients and practitioners and their staff with use of this product.

Questions for the Advisory Committee:

1) PhotoCure assessed efficacy for the treatment of nodular BCC with the following:
   a) 6 month post-treatment by histology only (not clinical) in two pivotal studies (no follow-up available) with 66 patients on MAL-PDT.
   b) 2 year clinical follow-up in open label studies in 86 patients.

Did PhotoCure adequately assess efficacy in the clinical studies?

2) Has PhotoCure adequately demonstrated and described the lesion preparation for use of this product?

3) Is the level of efficacy adequate, given the efficacy of treatments and products currently available for this indication?

4) Has the safety profile for this product been adequately assessed?

5) Is the contact sensitization rate acceptable?

6) Has PhotoCure identified, and conducted sufficient studies in, an appropriate patient population for the use of this product?

7) Given the safety and efficacy information, does the Committee find a favorable risk vs. benefit balance to support approval of this product?

8) What additional studies are needed? Are these studies needed before or after approval of the product?

9) For future development of this and/or other drug products for this indication, which measure(s) should be the key parameter(s) for efficacy, e.g., clinical evaluation and/or histological clearing? at what time point? recurrence rates? at what time point?

Appendix 1

Clinical Trials

Study Number	Location	Population Studied	Study Type	Number of Subjects per Study Arm	Curette-MAL-PDT and Comparator Regimen (if not vehicle controlled)
Vehicle-Controlled Multicenter Studies					
PC T307/00 Dec. 2000 to April 2002	USA	Primary Nodular BCC	Multicenter, double-blind, randomized, vehicle controlled	33 Curette-MAL-PDT 32 Curette-VEH-PDT	2 treatment sessions conducted 7 days apart, if partial response at 3 months follow-up another treatment cycle was given. 6 months after last PDT, all lesions were excised for histological evaluation.
PC T308/00 Oct. 2000 to Sept. 2002	Australia	Primary Nodular BCC	Multicenter, double-blind, randomized, vehicle controlled	33 Curette-MAL-PDT 33 Curette-VEH-PDT	2 treatment sessions conducted 7 days apart, if partial response at 3 months follow-up another treatment cycle was given. 6 months after last PDT, all lesions were excised for histological evaluation.
Open, Active-Controlled Studies					
PC T303/99 Ongoing Interim Report Initial: Apr. 2000 12m:Apr. 2002 24m: Nov. 2002	Europe	Primary Nodular BCC	Multicenter, open, randomized vs. surgical excision	52 Curette-MAL-PDT 49 Surgical Excision	2 treatment sessions conducted 7 days apart, if partial response at 3 months follow-up another treatment cycle was given./or A single surgical excision with margins from 1 to 5 mm.
PC T304/99 Ongoing Interim Report Initial: May 2002 12m: Nov. 2002 24m: Nov. 2002	Europe	Primary Superficial BCC	Multicenter, open, randomized vs. cryotherapy	60 Curette-MAL-PDT 58 Cryotherapy	1 treatment session conducted, if partial response at 3 months follow-up another treatment cycle was given consisting of 2 treatment session 7 days apart./or Min. 20 sec. double freeze-thaw cycle with hand-held liquid nitrogen spray. Response evaluation after 3 months. If non-complete response at the 3- month evaluation, cryotherapy was repeated with final response evaluation 3 months later (6 months after the initial treatment).
Open, Non-comparative Studies in Patients					
PC T205/98 Ongoing Interim Report Initial: Dec. 2000 12m: Dec. 2000 24m: Jun. 2002	Europe	Superficial and nodular BCC	Multicenter, open, non-comparative	94 Curette-MAL-PDT	2 treatment sessions conducted 7 days apart, if partial response at 3 months follow-up another treatment cycle was given. Clinical complete response verified by histology from a punch biopsy or a surgical procedure and a photograph.
PC T310/00 Ongoing Interim Report Initial: Jan. 2002 12m: Sept. 2002	Australia	Superficial and nodular BCC	Multicenter, open, non-comparative	102 Curette-MAL-PDT	2 treatment sessions conducted 7 days apart, if partial response at 3 months follow-up another treatment cycle was given. Complete response verified histologically, with punch biopsies in a grid pattern for lesions with pre-treatment diameter >10mm.

Appendix 2

Tables on Efficacy for Studies 307 & 308

Patients with Histological Complete Response – Sponsor's Analysis

Analyses	Curette-MAL-PDT	Curette-Veh-PDT	p-value [1]
Study 307			
ITT, n/N (%)	25/33 (76%)	11/32 (34%)	< 0.001
PP, n/N (%)	24/31 (77%)	11/32 (34%)	< 0.001
Study 308			
ITT, n/N (%)	22/33 (67%)	6/33 (18%)	< 0.001
PP, n/N (%)	21/29 (72%)	6/32 (19%)	< 0.001
[1] Cochran-Mantel-Haenszel test adjusting for center.			

Patient Response – FDA Analysis

	Curette-MAL-PDT	Curette-Veh-PDT	p-value [1]
Study 307			
1st PDT cycle *	17/33 (51.5%)	5/32 (15.6%)	0.003
Overall **	24/33 (73%)	8/32 (25%)	< 0.001
Study 308			
1st PDT cycle *	16/33 (48.5%)	3/33 (9.1%)	< 0.001
Overall **	21/33 (64%)	5/33 (15%)	< 0.001
[1] Cochran-Mantel-Haenszel test adjusting for center. * One cycle = 2 treatments; clinically clear at month 3 and histologically clear at month 6. ** For patients treated with the 1st PDT cycle, clinically clear at month 3 and histologically clear at month 6. For patients treated with 2 PDT cycles, clinically clear at month 6 and histologically clear at month 9. Two PDT cycles (4 treatments) were given to 10 patients on MAL and 8 patients on Veh in Study 307 and 5 patients on MAL and 4 patients on Veh in Study 308.			

Lesions with Histological Complete Response – Sponsor's Analysis

Analyses	Curette-MAL-PDT	Curette-Veh-PDT	p-value [1]
Study 307			
ITT, n/N (%)	32/41 (78%)	13/39 (33%)	< 0.001
PP, n/N (%)	31/39 (79%)	13/37 (35%)	< 0.001
Study 308			
ITT, n/N (%)	23/34 (68%)	7/36 (19%)	< 0.001
PP, n/N (%)	22/30 (73%)	7/33 (21%)	< 0.001
[1] Cochran-Mantel-Haenszel test adjusting for center.			

Lesion Response – FDA Analysis

	Curette-MAL-PDT	Curette-Veh-PDT	p-value [1]
Study 307			
1st PDT cycle *	19/41 (46%)	7/39 (18%)	0.007
Overall **	28/41 (68%)	10/39 (26%)	< 0.001
Study 308			
1st PDT cycle *	17/34 (50%)	4/36 (11%)	< 0.001
Overall **	22/34 (65%)	6/36 (17%)	< 0.001
[1] Cochran-Mantel-Haenszel test adjusting for center. * One cycle = 2 PDT treatments; clinically clear at month 3 and histologically clear at month 6. ** For lesions treated with the 1st PDT cycle, clinically clear at month 3 and histologically clear at month 6. For lesions treated with 2 PDT cycles, clinically clear at month 6 and histologically clear at month 9. Two PDT cycles (4 treatments) were given to 13 lesions on MAL and 9 lesions on Veh in Study 307 and 5 lesions on MAL and 4 lesions on Veh in Study 308.			

Patient Complete Response Rate after the 1st PDT Cycle by Center – Studies 307 and 308

Center	Study 307		Center	Study 308	
	Curette-MAL-PDT (n_bcc=41)	Curette-Veh-PDT (n_bcc=39)		Curette-MAL-PDT (n_bcc=34)	Curette-Veh-PDT (n_bcc=36)
30702	2/6 (33%)	1/7(14%)	**30801**	1/2 (50%)	0/3
30703	2/4 (50%)	0/2	**30802**	7/12 (58%)	3/12 (25%)
30704	0/5	1/5 (20%)	**30803**	NA	0/1
30705	1/2 (50%)	0/2	**30804**	2/2 (100%)	0/1
30706	5/9 (56%)	3/8 (38%)	**30805**	3/4 (75%)	0/4
30707	4/4 (100%)	0/4	**30806**	3/8 (38%)	0/7
30709	3/3 (100%)	0/4	**30807**	0/5	0/5
Total	17/33 (51.5%)	5/32 (16%)	**Total**	16/33 (48.5%)	3/33 (9%)
B-D Test [1]	0.045		**B-D test** [1]	0.468	

[1] B-D test for homogeneity of responses across centers.

Lesion Complete Response Rate after the 1st PDT Cycle by Center – Studies 307 and 308

Center	Study 307		Center	Study 308	
	Curette-MAL-PDT (n_bcc=41)	Curette-Veh-PDT (n_bcc=39)		Curette-MAL-PDT (n_bcc=34)	Curette-Veh-PDT (n_bcc=36)
30702	2/7 (29%)	1/8 (13%)	**30801**	1/2 (50%)	0/3
30703	2/4 (50%)	0/2	**30802**	8/13 (62%)	3/12 (25%)
30704	0/7	1/7 (14%)	**30803**	NA	0/1
30705	1/2 (50%)	1/3 (33%)	**30804**	2/2 (100%)	0/3
30706	6/13 (46%)	4/10 (40%)	**30805**	3/4 (75%)	1/5 (20%)
30707	5/5 (100%)	0/5	**30806**	3/8 (38%)	0/7
30709	3/3 (100%)	0/4	**30807**	0/5	0/5
Total	19/41 (46%)	7/39 (18%)	**Total**	17/34 (50%)	4/36 (11%)
B-D Test [1]	0.025		**B-D test** [1]	0.560	

[1] B-D test for homogeneity of responses across centers.

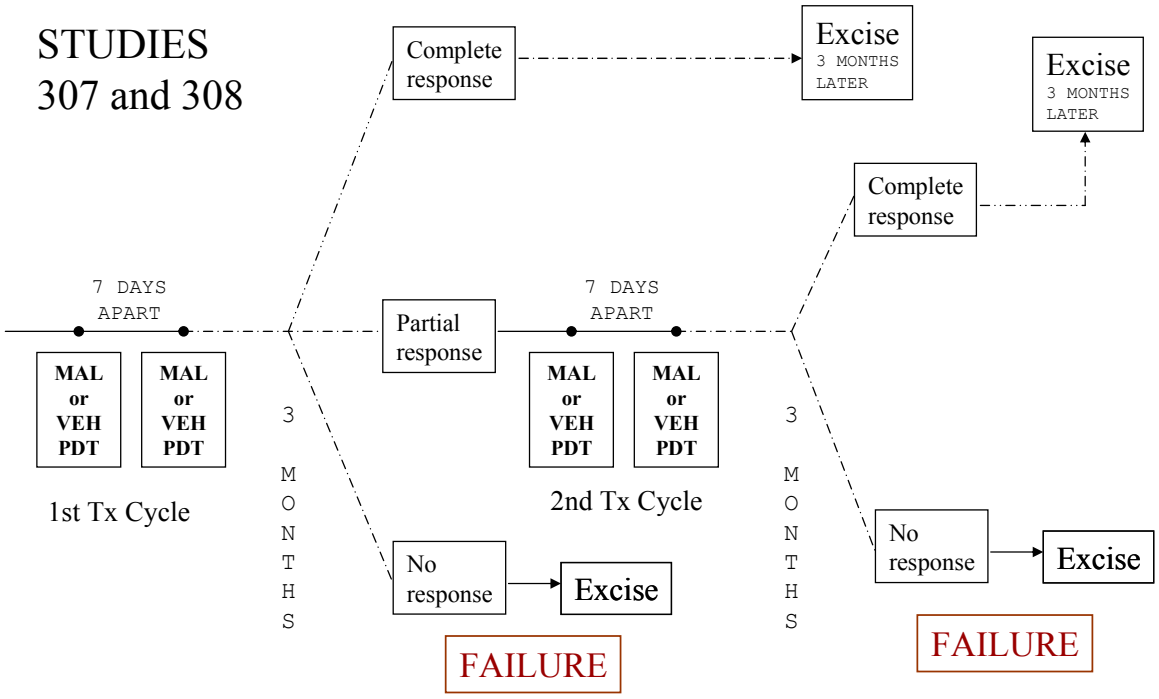
Sensitivity Analyses for Treatment-by-Center Interaction Patient Response Rate After the 1st PDT Cycle – Study 307

Endpoint	Analyses	Curette-MAL-PDT	Curette-Veh-PDT	p-value[1]	B-D test[2]
Patient Complete Response Rate	**All centers**	17/33 (51.5%)	5/32 (16%)	0.003	0.045
	Case (a)	12.64/33 (38%)	6.15/32 (19%)	0.114	0.673
	Case (b)	10/26 (38%)	5/24 (21%)	0.204	0.427
Lesion Complete Response Rate	**All centers**	19/41 (46%)	7/39 (18%)	0.007	0.025
	Case (a)	13.80/41 (34%)	8.80/39 (23%)	0.331	0.805
	Case (b)	11/33 (33%)	7/30 (23%)	0.452	0.568

Case (a) = Impute centers with extreme efficacy results by the mean response of the remaining centers
Case (b) = Exclude centers with extreme efficacy results (2 centers)
[1] Cochran-Mantel-Haenszel test adjusting for center.
[2] B-D test is for homogeneity of responses across centers.

Appendix 3

Flowchart for pivotal study design



Complete Response = disappearance of lesions - excision at 6-month for histology

Partial Response = lesion decreased by ≥ 50%) -2nd PDT cycle and excision at 9-month for histology

No Response or Progression = lesion decreased by < 50% or lesion increased by > 20% - excision at 3-month

Appendix 4

Analysis of the sensitization potential by Methyl aminolevulinate cream vs. vehicle vs. Aminolevulinic acid (ALA) vs. ALA vehicle

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