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Volume 3

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
24-Aug-92	QLT	012	Protocol Amendment	37,129	New Investigator, Change in Protocol.
15-Sep-92	QLT	013	Safety Report	37,129	Follow-up to Written Report.
04-Nov-92	QLT	014	Protocol Amendment	37,129	New Protocol (BPD 002); New Investigator.
09-Nov-92	QLT	015	Safety Report	37,129	Initial Report.
10-Nov-92	QLT	016	Information Amendment	37,129	Clinical.
14-Dec-92	QLT	017	Protocol Amendment	37,129	Change in protocol.
12-May-93	QLT	018	Information Amendment	37,129	Clinical.
21-May-93	QLT	019	Protocol Amendment	37,129	Change on Protocol BPD 002.
04-Jun-93	Regulatory Agency		General Correspondence	37,129	Dr. Williams did not have a problem with the proposed amendment to BPD 001 and the new IND for the treatment of genital warts should be submitted to the Antiviral Division.
04-Jun-93	Regulatory Agency		General Correspondence	37,129	A new IND is required for the treatment of genital warts and psoriasis program will be transferred to another division.
09-Jul-93	QLT	020	Protocol Amendment	37,129	Changes in protocol (BPD 001) Pharmacology, Clinical.
03-Aug-93	Regulatory Agency		General Correspondence	37,129	Psoriasis program should eventually switch from oncology to dermatology.

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Volume 4

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
12-Aug-93	QLT	021	Annual Report	37,129	Annual Report July 1992 to June 1993.
14-Oct-93	QLT		General Correspondence	37,129	BPD IND filing on genital warts should be submitted to the Antiviral Division.

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Volume 5-6

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
18-Nov-93	QLT	022	Information Amendment	37,129	Three toxicology reports to support the bolus administration of BPD-MA.

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Volume 7

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
23-Dec-93	QLT	023	Safety Report	37,129	IND Safety Report.
04-Feb-94	Regulatory Agency		General Correspondence	37,129	Update CIB due to additional info included.
08-Apr-94	QLT	024	Information Amendment	37,129	Change in US representation.
14-Apr-94	QLT	025	Protocol Amendment	37,129	Change in Protocol - New Investigator.
19-Apr-94	Regulatory Agency		Acknowledgement	37,129	Acknowledgement of receipt of Protocol Amendment - Serial #025.
26-May-94	Regulatory Agency		General Correspondence	37,129	Serial 025 Amendment; transfer of Psoriasis to new division.
02-Jun-94	Regulatory Agency		General Correspondence	37,129	Division for AMD indication.
02-Jun-94	Regulatory Agency		General Correspondence	37,129	Follow-up re: amendment #025.
02-Jun-94	Regulatory Agency		General Correspondence	37,129	Change in division for Topical Psoriasis.
07-Jun-94	Regulatory Agency		General Correspondence	37,129	Questions as to whether the BPD-MA was filtered.
14-Jun-94	Regulatory Agency		General Correspondence	37,129	Question Re: #025. New light source.
30-Jun-94	QLT	026	General Correspondence	37,129	Additional Laser source - Coherent Lambda Plus PDL2.
13-Jul-94	Regulatory Agency		General Correspondence	37,129	Confirmation of receipt of PDL2 laser submission.
15-Jul-94	QLT		Annual Report	37,129	Nonclinical Toxicology Studies. IND Annual Report (July 1992 - June 1993).
28-Jul-94	QLT	027	Protocol Amendment	37,129	response to FDA's comments re: Protocol Amendment #025.

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Volume 7

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
22-Aug-94	Regulatory Agency		General Correspondence	37,129	PDL2 submission acceptable; additional info requested.
25-Aug-94	Regulatory Agency		Fax	37,129	Addressed for FDA Oncology.

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Volume 8-13

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
14-Oct-94	QLT	028	Annual Report	37,129	Annual Report for July 1993 - June 1994.

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Volume 14-20

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
10-Oct-95	QLT	029	Annual Report	37,129	Annual Report to our IND for the use of BPD-MA (verteporfin) in cutaneous oncology for July 1994 to June 1995.

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Volume 21

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
18-Dec-95	QLT		General Correspondence	37,129	Fax to FDA to authorize cross-referencing.
18-Dec-95	QLT		General Correspondence	37,129	Serial Number 030, letter of authorization to cross-reference IND 37,129 with Dr. Yona Tadir's IND 49,174.
18-Dec-95	Regulatory Agency		Telephone Contact	37,129	FDA requests authorization to cross reference IND 37, 129 in conjunction with Dr. Tadir's CIN investigator sponsored study
20-Dec-95	Regulatory Agency		Receipt	37,129	Official receipt for the letter of authorization.
02-Feb-96	QLT		General Correspondence	37,129	Letter of Authorization to cross reference IND 37,129 in conjunction with investigator sponsored IND.
05-Feb-96	Regulatory Agency		General Correspondence	37,129	Receipt by FDA of February 2, 1996 submission to authorize cross-reference.
16-Apr-96	Regulatory Agency	032	Receipt	37,129	Receipt of cross-reference authorization submitted 16-Apr-96.
16-Apr-96	QLT	032	General Correspondence	37,129	Authorization to cross-reference IND 37,129 in conjunction with review of investigator sponsored IND (Z. Bernstein and co-investigators).
31-May-96	QLT		General Correspondence	37,129	Verbal Questions re Source of Hemin
31-May-96	QLT		General Correspondence	37,129	Verbal questions re source of hemin
03-Jun-96	QLT	033	General Correspondence	37,129	Letter of authorization for FDA to cross-reference Harimex DMF 11037
05-Jun-96	Regulatory Agency	033	Receipt	37,129	Acknowledgement of receipt of letter of authorization submitted June 3/96

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Volume 21

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
12-Feb-97	Regulatory Agency		General Correspondence	37,129	Reminder to send annual report.
10-Apr-97	QLT		E-mail	37,129	Apology for late annual report - will submit within next 2 weeks.

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Volume 22

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
24-Apr-97	QLT	034	Annual Report	37,129	Submission of Annual Report - Vol 1 of 3

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Volume 23

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
24-Apr-97	QLT	034	Annual Report	37,129	Submission of Annual Report - Vol 2 of 3

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Volume 24

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
24-Apr-97	QLT	034	Annual Report	37,129	Submission of Annual Report - Vol 3 of 3
09-Feb-98	QLT	035	Annual Report	37,129	Annual report for the period Feb 1/97 to Jan 31/98
10-Feb-98	QLT	035	Acknowledgement Letter	37,129	Acknowledgement of receipt of Annual Report.

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Volume 25

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
17-Aug-98	Regulatory Agency		Acknowledgement Letter	37,129	Acknowledgement of receipt of serial #036, annual report
17-Aug-98	QLT	036	Annual Report	37,129	Annual report covering the period from February 1, 1998 to date.
22-Sep-99	QLT	037	Annual Report	37,129	Submitted three copies of the annual report covering the period from August 17, 1998 to date.
24-Sep-99	Regulatory Agency		Fax	37,129	Acknowledgement of receipt of eighth annual report submitted Sept. 22, 1999.
09-Jun-00	QLT		E-mail	37,129	Initial FDA contact about photodynamic vaccination (PDV).
21-Jun-00	Regulatory Agency		E-mail	37,129	Questions re CMC and Device cross-referencing for PDV protocol.

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Volume 26-27

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
07-Jul-00	QLT	038	Protocol Amendment	37,129	Submitted a 2-volume protocol amendment for study VFI PDV 01.

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Volume 28

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
10-Jul-00	Regulatory Agency	038	Acknowledgement	37,129	Acknowledgement of receipt of protocol amendment to study VFI PDV 01 submitted Jul. 07/00.
11-Jul-00	Regulatory Agency		Telephone Contact	37,129	Paul Zimmerman called to check on the status of the PDV submission and to explain that there was a chance the submission may have to be sent to CBER and not CDER.
24-Jul-00	QLT		Telephone Contact	37,129	Follow-up on status of PDV submission.
01-Aug-00	Regulatory Agency		Telephone Contact	37,129	Questions from CBER pharm/tox reviewer on PDV study.
02-Aug-00	Regulatory Agency		Fax	37,129	Faxed adverse event summaries for Study BPD NMSC 01 as requested in connection with Protocol Amendment for Study VFI PDV 01.
11-Aug-00	Regulatory Agency		Telephone Contact	37,129	Follow-up on status of PDV protocol review.
22-Aug-00	QLT		E-mail	37,129	Follow up on CBER review of PDV protocol.
27-Sep-00	QLT	039	Protocol Amendment	37,129	Submitted protocol amendment to allow new investigator, Dr. Eric D. Whitman, to participate in Study VFI PDV 01.
28-Sep-00	Regulatory Agency	039	Acknowledgement	37,129	Acknowledgement of receipt of protocol amendment to allow new investigator, Dr. Eric D. Whitman, to participate in Study VFI PDV 01 submitted Sept 27, 2000.
05-Oct-00	QLT	040	Information Amendment	37,129	Submitted two pharmacology reports which provide new nonclinical information: QLT Report PH-00016 & PH-00013.
26-Oct-00	QLT		Annual Report	37,129	Submitted Annual Report covering the period Sept 23, 1999 to Oct 6, 2000.

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Volume 28

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
30-Oct-00	Regulatory Agency		Acknowledgement	37,129	Acknowledgement of receipt of Annual Report covering the period of Sept 23, 1999 to Oct 6, 2000 submitted Oct 26, 2000.
23-Jan-01	QLT	042	Protocol Amendment	37,129	Submitted protocol amendment to allow new investigator, Dr Rene Gonzalez, to participate in Study VFI PDV 01.
25-Jan-01	Regulatory Agency	042	Acknowledgement	37,129	Acknowledgement of receipt of protocol amendment for new investigator, Dr Rene Gonzalez, who is to participate in Study VFI PDV 01 submitted Jan 23, 2001.
29-Jan-01	Regulatory Agency		Telephone Contact	37,129	PDV Clinical Supplies, US Custom's Holdup.
30-Jan-01	QLT		Fax	37,129	Request for product information for release by US Customs of PDV chemical supplies.
30-Jan-01	Regulatory Agency		Telephone Contact	37,129	Request for product information for release by US customs of PDV clinical supplies.
05-Feb-01	QLT	043	Protocol Amendment	37,129	Submitted protocol amendment with copies of amended protocol for Study VFI PDV 01.
06-Feb-01	Regulatory Agency	043	Acknowledgement	37,129	Acknowledgement of receipt of protocol amendment with copies of amended protocol for Study VFI PDV 01 submitted Feb 5, 2001.
07-Mar-01	QLT	044	Protocol Amendment	37,129	Submitted protocol amendment for new investigator, Dr Sanjiv S Agarwala, who is to participate in Study VFI PDV 01.
12-Apr-01	QLT	045	Safety Report	37,129	Submitted initial safety report (QLT Event C2001147 Study VFI PDV 01) for a serious adverse reaction of allergic reaction, hypersensitivity.

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Volume 28

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
13-Apr-01	Regulatory Agency	045	Acknowledgement	37,129	Acknowledgment of receipt of initial safety report (AE # C2001147 Study VFI PDV 01) submitted Apr 12, 2001.
08-May-01	QLT	046	Safety Report	37,129	Submitted follow-up safety report (QLT AE C2001147) concerning a serious adverse reaction of chest pain and shortness of breath (Study VFI PDV 01).
09-May-01	Regulatory Agency	046	Acknowledgement	37,129	Acknowledgement of receipt of follow-up safety report (QLT AE C2001147) submitted May 8, 2001.
05-Oct-01	QLT	047	Information Amendment	37,129	Submitted clinical information amendment notification that enrollment into Phase I/II study (VFI PDV 01) has been discontinued.
09-Oct-01	Regulatory Agency		Acknowledgement	37,129	Acknowledgement of receipt of clinical information amendment notification that enrollment into Phase I/II study, VFI PDV 01, has been discontinued.
01-Nov-01	QLT	048	Annual Report	37,129	Submitted annual report covering the period Oct 7, 2000 - Oct 30, 2001.
06-Nov-01	Regulatory Agency		Acknowledgement	37,129	Acknowledgement receipt of IND annual report covering the period Oct 7, 2000 - Oct 30, 2001.

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Volume 29

16-Feb-04

Date	Initiator	ID #	Type	Submission Reference Number:	Description
11-Dec-02	QLT	049	Annual Report	37,129	Submitted 2002 annual report covering the period Oct 31, 2001 to Nov 30, 2002.
12-Dec-02	Regulatory Agency	049	Acknowledgement	37,129	Acknowledgement of receipt of 2002 annual report covering the period Oct 31, 2001 to Nov 30, 2002.
13-Feb-03	QLT	050	Information Amendment	37,129	Submitted a clinical final report entitled: "A Phase I/II Uncontrolled, Open-Label Study of the Safety and Efficacy of Photodynamic Vaccination [Verteporfin Photodynamic Therapy plus ENHANZYN Immunostimulant (Detox B-SE)] in Patients with Stage III/IV Malignant Melanoma".
20-Feb-03	Regulatory Agency	050	Acknowledgement	37,129	Acknowledgement of receipt of clinical information amendment; final report for VFI PDV 01 submitted Feb. 13/03.
23-Jan-04	QLT	051	Annual Report	37,129	Submitted a letter as our annual report for the period December 1, 2002 to November 30, 2003. No studies were conducted therefore nothing to report. Wish to keep this IND open and continue to evaluate potential new indications in oncology.
27-Jan-04	Regulatory Agency	051	Acknowledgement	37,129	Acknowledgement of receipt of IND Annual Report.

Clinical Study Report — BPD 001

Verteporfin for Injection

**Photodynamic Therapy with
Benzoporphyrin Derivative Monoacid A Ring (BPD-MA) in the
Treatment of Malignant Cutaneous Lesions**

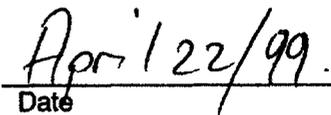
January 22, 1999

This Study Report is written as an accurate record of the conduct and the results of the study by:

Clinical Director:



Andrew Strong, PhD

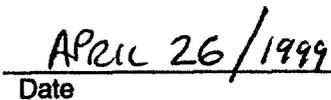


Date

PK Director:

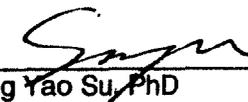


Jean-Marie Houle, PhD

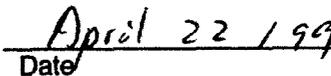


Date

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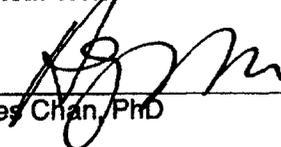


Xiang Yao Su, PhD

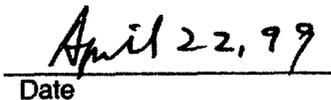


Date

Medical Writer:



Agnes Chan, PhD



Date

This study was conducted in accordance with the clinical research guidelines established by the HPB Drugs Directorate, the Medical Research Council of Canada, the basic principles defined in the U.S. 21 CFR Parts 50, 56, and 312, and the principles enunciated in the Declaration of Helsinki (Hong Kong, 1989).

QLT PhotoTherapeutics Inc.
520 West 6th Avenue
Vancouver, British Columbia
Canada V5Z 4H5

QUALITY ASSURANCE REVIEW STATEMENT

Study Number and Title: BPD 001, Photodynamic Therapy with Benzoporphyrin Derivative Monoacid A Ring (BPD-MA) in the Treatment of Malignant Cutaneous Lesions

The content of this report has been reviewed against the data listings, summary tables, protocol, and amendments for accuracy and completeness by:



Michele Gervais, BSc
Quality Assurance

Apr 22 / 99
Date

APPROVAL STATEMENT

This Clinical Study Report of Study BPD 001, entitled "Photodynamic Therapy with Benzoporphyrin Derivative Monoacid A Ring (BPD-MA) in the Treatment of Malignant Cutaneous Lesions", is an accurate record of the conduct and the results of the study.

Approved by:



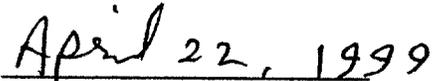
Noel Buskard, MD, FRCP, FACP
Safety and Medical Officer



Date



Mohammad Azab, MD
Vice President, Clinical Research



Date

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SYNOPSIS

Name of Sponsor/Company: QLT PhotoTherapeutics Inc	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: Verteporfin for Injection		
Name of Active Ingredient(s): Verteporfin (benzoporphyrin derivative mono-acid A ring)		
Study Number and Title:	BPD 001: Photodynamic Therapy with Benzoporphyrin Derivative Monoacid A Ring (BPD-MA) in the Treatment of Malignant Cutaneous Lesions.	
Study Investigator(s) and Center(s):	Drs. H. Lui, D. McLean (Vancouver, Canada) Dr. R. Anderson (Boston, USA) Dr. L. Hruza (St. Louis, USA)	
Date of First Patient Enrolled:	November 15, 1991	
Date of Last Patient Enrolled:	March 27, 1995	
Date of Last Patient Completed:	July 10, 1995	Clinical Phase: Phase I/II
Study Objective(s):	<ol style="list-style-type: none"> To estimate the duration of skin photosensitivity on normal skin to broad spectrum light. To estimate a maximum tolerated drug and light dose (MTD) combination for local nontumor (peritumoral) skin response and for systemic toxicity of verteporfin. To evaluate patient response as a function of drug and light doses. To assess the pharmacokinetic profile of verteporfin in humans. 	
Study Description (Methods and Investigational Plan):		
Design	This was an open-label, uncontrolled, ascending dose study to evaluate the safety of Verteporfin for Injection and light.	
Population	Twenty-seven to 45 patients of either gender with at least one cutaneous lesion caused by metastatic malignancy, basal cell carcinoma, squamous cell carcinoma, or Kaposi's sarcoma were to be treated. Patients must have been over 18 years of age.	
Treatment (Identity of Investigational Product)	Patients received a 45-minute IV infusion of verteporfin (0.15 to 0.5 mg/kg). Treatment fields (10 cm ²) containing cutaneous lesion(s) of at least 0.5 cm in linear dimension were exposed to 25-150 J/cm ² of 690±3 nm light, 1.5 to 6 hours after the start of verteporfin infusion. Patients were followed for 3-months posttreatment. Batch R1186-102 of Verteporfin for Injection was used in this study.	
Study Variables		
<i>Primary</i>	<ol style="list-style-type: none"> Duration of skin photosensitivity; number of days post verteporfin infusion when the minimal erythematous dose (MED) of broad spectrum light had returned to baseline level. 	
<i>Secondary</i>	<ol style="list-style-type: none"> Systemic toxicity profile of verteporfin according to the National Cancer Institute (NCI) common toxicity criteria. Photodynamic Therapy (PDT)-induced skin reaction on normal peritumoral skin site (i.e. normal skin surrounding the tumors within the treatment field). Tumor and patient response. Pharmacokinetic profile between 0 and 96 hours post verteporfin infusion. 	

<p>Study Description (cont'd) Assessments</p> <p>Statistical Methods</p>	<p>Duration of skin photosensitivity was evaluated by assessing each patient's MED prior to treatment and then daily after treatment.</p> <p>Systemic toxicity of verteporfin was assessed clinically by recording of all adverse events and biologically by blood and urine analyses at Days 1, 2, 3, and 7 post drug administration.</p> <p>PDT-induced skin reactions in the peritumoral area were assessed by clinical examination of the treatment sites at all follow-up visits post PDT using the skin toxicity scale.</p> <p>Tumor response was evaluated by measuring the changes in tumor size at each of the follow-up visits. Biopsy samples were obtained from tumors that completely responded.</p> <p>Pharmacokinetic parameters were assessed from blood samples collected prior to, during, and up to 96 hours after the start of infusion.</p> <p>Skin photosensitivity duration was determined using descriptive statistics. The measured photosensitivity (1/MED) and time was evaluated by regression analyses to assess the rate of photosensitivity decline.</p> <p>Systemic safety and peritumoral PDT-induced skin reaction was analyzed using descriptive statistics.</p> <p>Tumor response rates were analyzed in terms of tumor type, verteporfin dose, light doses, and time of final assessment by logistic regressions using lesions as the experimental unit. Patient response rate was determined by aggregating tumor response.</p> <p>Compartmental and non compartmental methods were used to calculate the pharmacokinetic parameters, based on observed plasma concentrations.</p>
<p>Study Results: Patient Disposition and Demography</p> <p>Protocol Deviations</p> <p>Efficacy Results</p> <p>Pharmacokinetic Results</p>	<p>This study included 35 patients (17 males and 18 females between the ages of 23 and 80) receiving a total of 40 courses of verteporfin and light. Thirty-one received one course of therapy, 3 patients received 2 courses and 1 patient received 3 courses. Treatment interval between courses for these patients was at least 3 months. Ten of the 35 patients enrolled had Basal Cell Carcinoma (BCC), 9 had nevoid BCC syndrome and 1 had Bowen's disease. The remaining 15 patients had metastatic skin tumors. A total of 182 tumors (104 primary and 78 metastatic) were treated.</p> <p>No major deviations occurred that would lead to exclusion of patients from the analysis.</p> <p>The overall patient objective response (complete + partial) rate was 80% for primary skin tumor patients and 67% for metastatic tumor patients. The overall tumor (lesion) objective response (complete + partial) rate was 89% for primary tumors and 82% for metastatic tumors.</p> <p>Logistic regression analysis was performed to evaluate the relationship between complete tumor response rate (CR_T) and variables such as tumor type, drug dose, and light dose. A drug dose of ≥ 0.35 mg/kg followed by a light dose of ≥ 50 J/cm² were associated with the probability of a CR_T rate of $\geq 95\%$ in primary tumors and $\geq 80\%$ in metastatic tumors.</p> <p>Pharmacokinetic data was available from 22 sets of plasma samples, from 21 patients who received a single intravenous dose of 0.15, 0.20, 0.25, 0.375, or 0.50 mg/kg of verteporfin.</p> <p>At all doses investigated, the maximal plasma concentration is observed at the end of the infusion (ranged from 0.68 – 1.87 μg/mL for doses between 0.15 mg and 0.50 mg/kg) and was followed by rapid decline (alpha half-life ranging from 0.25 to 0.58 hours and beta half-life of 4.7 to 6.3 hours). The extent of exposure, as depicted by the Area Under the Curve (AUC), increases linearly and proportionally as a function of dose. The volume of distribution and total body clearance shows no change in the dose range studied. The two regioisomers of verteporfin behaved similarly.</p>

<p>Study Results (cont'd) Safety Results</p>	<p>Safety data is summarized in the table below:</p> <table border="1" data-bbox="683 289 1377 544"> <thead> <tr> <th></th> <th>Treated Patients n=35</th> </tr> </thead> <tbody> <tr> <td>Patients with any adverse event</td> <td>35</td> </tr> <tr> <td>Patients with associated AE^a</td> <td>35</td> </tr> <tr> <td>Deaths from any cause</td> <td></td> </tr> <tr> <td> ≤ 30 days post PDT</td> <td>0</td> </tr> <tr> <td> > 30 days post PDT</td> <td>4</td> </tr> <tr> <td>Deaths due to AE</td> <td>1^b</td> </tr> <tr> <td>Withdrawal due to an adverse event</td> <td>0</td> </tr> <tr> <td>Other serious AE</td> <td>1</td> </tr> </tbody> </table> <p>^a Probably or possibly related to therapy including local treatment site adverse events. ^b Considered to be not related to study treatment.</p> <p>No clinically significant systemic adverse events were reported. Most frequent treatment-related local adverse events of the treatment field were warmth and burning during light application (49% and 23% of patients, respectively), and pain and edema after light treatment (57% and 26% of patients, respectively). These events are consistent with the pharmacological action of PDT. Most of the events were mild to moderate, completely reversible, and easily controlled by analgesic treatment.</p> <p>None of the patients in this study experienced a Grade-2 treatment-related systemic toxicity. All drug- and light-dose regimens were associated with Grade 3 and 4 PDT-induced skin reactions except for 2 regimens: 0.15 mg/kg drug + 150 J/cm² light and 0.25 mg/kg drug + 50 J/cm² light. Therefore these drug regimens represent two MTDs by the protocol's definition.</p>		Treated Patients n=35	Patients with any adverse event	35	Patients with associated AE ^a	35	Deaths from any cause		≤ 30 days post PDT	0	> 30 days post PDT	4	Deaths due to AE	1 ^b	Withdrawal due to an adverse event	0	Other serious AE	1
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> 30 days post PDT	4																		
Deaths due to AE	1 ^b																		
Withdrawal due to an adverse event	0																		
Other serious AE	1																		
<p>Duration of Skin Photosensitivity Results</p>	<p>All patients had baseline MED >215 J/cm² of broad spectrum light. At verteporfin doses of 0.15 mg/kg and 0.50 mg/kg, the mean time for patients to have minimal erythematous reaction when exposed to 215 J/cm² was 2 and 6.7 days posttreatment respectively.</p>																		
<p>Study Conclusions</p>	<ol style="list-style-type: none"> 1. The time for patients to return to MED value of 215 J/cm² (which is equivalent to 0.5-1 hour of midday exposure in the summer in New Mexico) was approximately 6.7 days at the highest drug dose studied (0.50 mg/kg). Hence, the actual time required for a patient infused with 0.50 mg/kg of verteporfin to avoid long bright sunlight exposure should be less than 6.7 days. Duration of skin photosensitivity is dose-dependent as it was shorter at lower doses (2 days at 0.15 mg/kg drug dose). 2. Grade-3 and 4 PDT-induced peritumoral skin reactions were observed in many patients. However, the treatment fields healed well with good cosmetic outcome. Skin reaction could be limited in future studies by reducing the circumferential peritumoral area to 3-4 mm, which is the standard margin used in surgical excision of cutaneous tumors. No major drug-related systemic toxicity was encountered. 3. High complete tumor and patient response rate was observed in several drug- and light-dose combinations. The recommended drug and light doses to achieve highest response are ≥0.35 mg/kg and ≥50 J/cm² respectively. 4. The pharmacokinetics of verteporfin, after a single 45-minute IV infusion, exhibits simple pharmacokinetics that are highly predictable. With an apparent elimination half-life of 5-6 hours, verteporfin is rapidly cleared from the body and should not result in accumulation with the intended dose regimens that call for single doses or doses separated by a minimum of 1 week. 																		

LIST OF ABBREVIATIONS

Alpha	Apparent distribution rate constant obtained by compartmental analysis
ALT	Alanine transferase
APDL	Argon-ion pumped-dye laser
AST	Aspartate transaminase
AUC ₀₋₂₄	Area under the plasma drug concentration vs time curve from zero to last measurable concentration
AUC _{inf}	Area under the curve from zero to infinity
AUMC	Area under the first moment of plasma versus time curve
Beta	Apparent elimination rate constant obtained by compartmental analysis
BCC	Basal cell carcinoma
BCNS	Nevoid basal cell carcinoma (basal cell nevus syndrome)
BPD-MA	benzoporphyrin derivative monoacids A ring (verteporfin)
BUN	Blood urea nitrogen
CL	Total body clearance
cm ²	Square centimeter
C _{max}	Maximum measured plasma concentration over the time span specified
CNS	Central nervous system
CR _P	Patient complete response
CR _T	Tumor complete response
ECG	Electrocardiogram
Erythema	Redness of the skin caused by congestion of the skin capillaries
GGT	γ-Glutamyltransferase
IRB/ERB	Institutional Review Board / Ethical Review Board
J	joules
kg	kilogram
LDH	Lactate dehydrogenase
MAT	Mean absorption time
MED	Minimal Erythematous Dose
mg	milligrams
MRT	Mean residence time
MTD	Maximum Tolerated Dose
mW	milliWatts
NLIN	Procedure NLIN of SAS
NMSC	Nonmelanoma skin cancer
NSAID	Nonsteroidal anti inflammatory drug
PD _P	Patient progressive disease
PDT	Photodynamic Therapy
PD _T	Tumor progressive disease
PR _P	Patient partial response
PR _T	Tumor partial response
RBC	Red blood cell count
SCC	Squamous cell carcinoma
SD _P	Patient stable disease
SD _T	Tumor stable disease
T _½	Apparent plasma elimination half-life obtained by non-compartmental analysis
TF	Treatment field
UV	Ultraviolet
UVA	Ultraviolet A
V _{ss}	Apparent volume of distribution
WBC	White blood cell count

1. INTRODUCTION

Nonmelanoma skin cancer (NMSC) currently accounts for approximately one-third of all cancers, with increased incidence expected as the population ages. Basal cell and squamous cell skin cancers account for more than 900,000 new cases of cancer annually in the US (1) and over 2.7 million cases estimated worldwide (2).

Most NMSCs are basal cell carcinomas (BCC), which occur mainly on sun-exposed areas such as the face, especially the nose, the nasolobial fold and the inner canthus areas. BCC can be presented as solitary or multiple lesions. The tumors have a tendency to be locally destructive and rarely metastasize. Nevoid BCC syndrome (BCNS) is a familial autosomal-dominant disorder caused by a loss of heterozygosity of the 9q chromosome. Skin lesions usually develop in large numbers between puberty and age 35. They may become nodular or ulcerative and aggressive (2).

Squamous cell carcinomas (SCC), which represent the remaining 20-25% of NMSC, are fast growing and prone to metastasize. Squamous carcinoma in situ (Bowen's disease) is an intraepidermal SCC that may involve any area of the skin, but tends to favor sun-exposed areas of the face, neck, and extremities. In one-third of patients, the lesions may be multiple. Bowen's lesions may progress to invasive SCC. The reported incidence rate is about 3 to 5% (3).

Cutaneous or subcutaneous cancer can also occur as a consequence of disease metastatic from other sites. The most common carcinomas metastatic to the skin are metastatic breast carcinoma, metastatic renal carcinoma, metastatic carcinoma of the gastrointestinal tract, and metastatic bronchogenic carcinoma.

Current treatments for these cutaneous skin cancers include surgery, Moh's micrographic surgery, cryosurgery, electrodesiccation and curettage, radiation, and carbon dioxide laser. Current therapies achieve response rates ranging from 80 to 96%, with recurrence rates within 5 years ranging from approximately 5% to as high as 50%. Rates for both response and recurrence vary by therapy, by lesion type, and by anatomic location (4).

Photodynamic therapy (PDT) is a two-step process consisting of administration of a photosensitizer such as verteporfin, followed by light irradiation. The wavelength of light normally used for activating verteporfin is 690 nm. At clinical doses used for PDT, verteporfin itself is not cytotoxic. However, it produces local cytotoxic agents when activated by light in the presence of oxygen (5).

Verteporfin, like many other photosensitizers, tends to accumulate in malignant cells and the neovasculature (6), making PDT an effective approach for the treatment of cancerous tissue

at sites that can be illuminated directly with light. PDT with verteporfin and 690 nm light is potentially an effective therapy for treating skin cancer.

This report gives the results of the first human study of verteporfin. The objectives of this Phase I/II study were to evaluate the systemic toxicity of verteporfin, to evaluate PDT-induced skin reaction in the peritumoral area, to estimate the duration of normal skin photosensitivity to broad spectrum light after verteporfin infusion, to determine the pharmacokinetic profile of verteporfin, and to assess the potential efficacy of PDT (with various combinations of verteporfin and 690 nm light) in treating cutaneous lesions.

Data obtained from this study will be used for designing future protocols in the treatment of cutaneous lesions.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

CVs of Lead Investigators: Appendix D.3

Country	Investigator	Study Center	Number of Patients Enrolled
Canada	Drs. Harvey Lui/David McLean	Vancouver General Hospital Vancouver, BC Canada	12
U.S.A	Dr. Rox Anderson	Wellman Laboratories of Photomedicine Massachusetts General Hospital Boston, MA USA	19 ^a
	Dr. Luciann Hruza	Barnes West County Hospital St. Louis, MI USA	4 ^b

^a 1 patient received two courses of PDT treatment.

^b 2 patients received two courses of PDT treatment and 1 patient received 3 courses of PDT.

Initially, the study involved only one center with Dr. Rox Anderson of the Wellman Laboratories of Photomedicine, Massachusetts General Hospital, Boston, Massachusetts, as the Principal Investigator. Later, the two co-investigators involved in the study, Dr. Harvey Lui and Dr. Luciann Hruza, moved and subsequently established two new sites in Vancouver and St. Louis respectively.

The study was monitored by representatives of QLT PhotoTherapeutics Inc. (QLT) and the National Medical Research Corporation (NMRC¹, a contract research organization). The clinical trial supply management was provided by QLT. Patients were assigned to treatment by the QLT PhotoTherapeutics Inc. Clinical Research Coordinators (Ingmari Bysse or Kelly Smith) according to the Drug and Light Dose Schema.

The same contract research organization (NMRC), was hired to perform data entry procedures for the first 26 patients. QLT PhotoTherapeutics Inc. assumed the responsibility for the remaining patients.

The Study Director was Andrew Strong, PhD (QLT PhotoTherapeutics Inc.) Statistical analysis was conducted by Xiang Yao Su, PhD (QLT PhotoTherapeutics Inc.)

¹ National Medical Research Corporation
25 Main Street
Hartford, Connecticut USA 06106
(203) 724-0091

The laboratory assessments were done at the investigational sites by their accredited laboratories.

Curriculum vitae of all Lead Investigators are provided in Appendix D.3.

3. STUDY ETHICAL CONSIDERATIONS

3.1 Institutional Review Boards (IRB)

List of IRB Approvals: Appendix D.4.1

The study protocol, all amendments, informed consent forms were reviewed by the Institutional Review Boards at all three sites (Boston, Vancouver, St. Louis). A list of the IRB approvals from these sites is provided in Appendix D.4.1.

3.2 Ethical Conduct of Study

This study was conducted in accordance with the clinical research guidelines established by the Canadian HPB, the Medical Research Council of Canada, the basic principles defined in US 21 CFR (Parts 50, 56, and 312) and the principles enunciated in the Declaration of Helsinki (Hong Kong, 1989).

3.3 Patient Information and Consent

Sample Patient Informed Consent: Appendix D.4.2

The Investigator or his/her delegate explained full details of the study protocol and the study procedures to potential participants prior to study enrollment. Patients signed an Informed Consent form US 21 CFR Part 50, and was approved by the Institution's IRB. A sample patient Informed Consent form is provided in Appendix D.4.2.

4. STUDY OBJECTIVES

The objectives of the study were as follows:

1. To estimate the duration of skin photosensitivity on normal skin to broad spectrum light.
2. To estimate a maximum-tolerated drug and light dose combination for local nontumor (peritumoral) skin response, including local photosensitivity of normal skin, and for systemic toxicity of verteporfin.

Maximum tolerated dose (MTD) was determined by combining systemic and PDT-induced skin toxicity. Thus, the objective could be separated into two parts, namely:

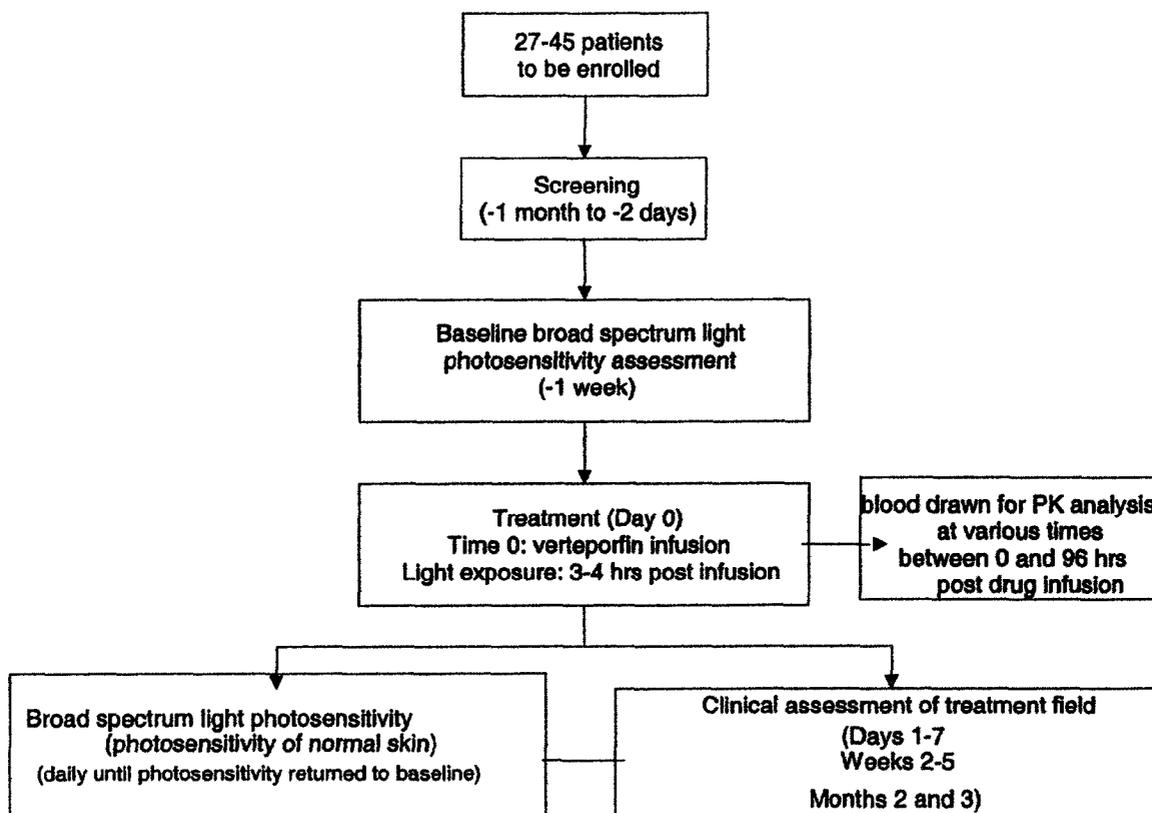
- to evaluate the systemic toxicity of verteporfin; and
 - to assess PDT-induced skin reactions in the normal skin, which included normal skin in the peritumoral area within the treatment field;
3. To evaluate patient response as a function of drug and light doses; and
 4. To assess the pharmacokinetic profile of verteporfin in humans.

5. STUDY DESCRIPTION (METHODS AND INVESTIGATIONAL PLAN)

Protocol and Protocol Amendments: Appendix D.1
Sample Case Report Form: Appendix D.2
Drug and Light Dose Allocation Guidelines: Appendix D.6.1

5.1 Overall Study Design

This was an open-label, ascending-dose study with various combinations of verteporfin and light doses. In the Protocol, ascending drug doses of 0.25, 0.50, and 0.70 mg/kg and light doses of 50, 100, and 150 J/cm² at 690 nm wavelength were planned. Patients had to have at least 1 cutaneous lesion caused by metastatic disease, basal cell carcinoma or squamous cell carcinoma. Each patient was to receive a single drug-light dose on all lesions. Patients were followed for 3 months. A schematic summary of the Protocol is presented below (Flow Chart 1).



FLOW CHART 1. Schematic Summary of Study BPD 001

Originally, there were only 9 steps in the ascending drug and light dose schedule (i.e., 3 drug doses and 3 light doses). Patients were consecutively assigned to these steps according to guidelines outlined in the Protocol (Appendix D.6). However, upon reaching Step 4 (0.5 mg/kg

verteporfin + 50 J/cm² of light), a Grade-4 skin reaction in the peritumoral area was observed in 2 out of 3 patients and drug escalation was terminated. Subsequent patients were given lower drug doses. At the end of the study, twelve drug-light combinations involving 6 drug doses (0.15, 0.20, 0.25, 0.30, 0.375, and 0.50 mg/kg) and 6 light doses (25, 50, 75, 100, 125, and 150 J/cm²) were used. Time for light applications was between 1.5 and 6 hours post the start of drug infusion (Amendment 5). The study protocol and amendments are included in Appendix D.1.

Since this was the first study of verteporfin in humans, emphasis was placed on safety assessments such as the systemic toxicity of the drug and the severity of peritumoral skin reactions to PDT. Results of the laboratory tests and adverse event reporting planned allowed for an estimation of systemic toxicity. Assessing of the peritumoral area after PDT allowed estimation of the PDT skin reactions in these presumably normal tissues.

Verteporfin, like all other photosensitizers, induces skin photosensitivity. Therefore, the evaluation of the duration of skin photosensitivity was considered one of the objectives in this study. Photosensitivity testing was accomplished using an Oriel broad light spectrum solar simulator (UVA/visible). A light dose of 215 J/cm² was used as the maximum light dose. The data gathered from this study would provide information regarding the maximum duration of normal skin photosensitivity resulting from verteporfin infusion.

The study design allowed for some analysis of efficacy. Following the response of the lesions in the treatment fields by measuring them post PDT would give an idea of the potential efficacy of verteporfin against skin cancer lesions.

Serial blood samples were obtained in some patients over the 96 hours post-infusion to allow determination of pharmacokinetic parameters after various doses of verteporfin.

5.2 Study Population

5.2.1 Number of Patients

The Protocol estimated that 27 to 45 patients would be enrolled. Three to six patients were to be assigned to each of the 9 drug-light dose combinations and ascending doses were to be continued until a maximum-tolerated dose was achieved.

5.2.2 Inclusion Criteria

The following patients were considered eligible for enrollment:

- 1) Patients with at least one cutaneous lesion caused by the following:
 - metastatic disease
 - basal cell carcinoma
 - squamous cell carcinoma
 - Kaposi's sarcoma (Amendment 3, February 1992)
- 2) Basal cell carcinoma could have been de novo or recurrent. Squamous cell carcinoma could have been recurrent or considered inappropriate for treatment with standard therapy because of the potential for disfigurement. Patients with basal cell nevus syndrome were eligible (Amendment 2, September 1991). Patients undergoing anti-HIV therapies were eligible (Amendment 3, February 1992).
- 3) Patients who had a greater number of lesions than could be included in the treatment fields of 10 cm² each could have been enrolled if the lesions outside the treatment fields were asymptomatic. (However, patients with de novo basal cell carcinoma with lesions outside the treatment fields that were symptomatic could have been enrolled, since these patients would have surgical excision one week after PDT treatment or at the Investigator's discretion (Amendment 2, September 1991).
- 4) Each lesion must have been at least 0.5 cm in two perpendicular dimensions, and the maximum diameter of a lesion must not have exceeded 3.0 cm. The total area of the treatment field must have been <10 cm², including a torus of normal skin with a breadth of 1 cm at some point. If the patient had a Morphea-form type, margins of normal skin around the lesions must have been at least 1 cm.
- 5) Patients must have had a Karnofsky Performance Status of at least 70.
- 6) Patients must have had a life expectancy of at least 6 months.
- 7) Patients must have been 18 years of age or older.
- 8) Patients could have been male or female. Female patients had to be post menopausal or surgically sterile.

- 9) Patients must have been considered reliable by the Investigator and be able and willing to stay in the hospital for treatment and observation for approximately 4 days. They must also have agreed to return regularly for follow-up over a period of 3 months (Amendment 4, July 1992). Amendment 5 (June 1993) allowed inclusion of outpatients at the Investigator's discretion.
- 10) Patients must have been capable of giving written evidence of informed consent.

5.2.3 Exclusion Criteria

- 1) Patients with skin lesions that were greater than 1 cm in depth, and where the lesion(s) within a treatment field of maximum size 10 cm² was (were) <0.5 cm in two perpendicular dimensions.
- 2) Patients who had symptomatic lesions outside the treatment fields, with the exception of de novo basal cell carcinoma patients, since these patients would have surgical excision after verteporfin treatment (Amendment 2, September 1991).
- 3) Patients who had porphyria or other porphyrin sensitivity, hypersensitivity to sunlight or bright artificial light.
- 4) Patients who had other serious dermatological conditions or an uncontrolled infection.
- 5) Patients with metastatic malignant melanoma that were melanotic.
- 6) Patients with invasive squamous cell carcinoma (Amendment 3, February 1992).
- 7) Patients with skin types IV, V, and VI.
- 8) Patients with a history of seizure disorders.
- 9) Patients with brain metastasis.
- 10) Patients with neuropathy.
- 11) Patients with serious ophthalmic disease.
- 12) Patients with impaired renal function (serum creatinine >2 mg/L).
- 13) Patients with a history of diffuse liver disease and/or abnormal liver function tests at baseline (Amendment 4, July 1992).

- 14) Patients with: WBC $<3 \times 10^9$ g/L, platelet count $<100 \times 10^9$ g/L, prothrombin >1.5 times the upper limit of normal, or hemoglobin <110 g/L.
- 15) Patients with unstable cardiovascular disease (Amendment 3, February 1992).
- 16) Patients who were concurrently being treated with radiotherapy, immunotherapy, chemotherapy, hormonal therapy, or had received radiotherapy or chemotherapy within the previous 6 weeks, or had received PHOTOFRIN® within the past 12 weeks.
- 17) Patients receiving glucocorticoid therapy or long term therapy with NSAID's.
- 18) Patients who had previous squamous cell carcinoma which would, in the opinion of the Investigator, be adequately and satisfactorily treated with present standard treatment modalities, and for whom photodynamic therapy would not be a reasonable option (Amendment 2, September 1991).

5.2.4 Removal of Patients from Treatments or Assessments

Investigators could remove patients from the study and offered alternative therapy throughout the study if there was progression of disease, or if evidence of healing of lesions had not occurred after 2 weeks.

5.3 Study Treatments

5.3.1 Treatments Administered

This was the first human study of verteporfin. Doses were selected based on preclinical pharmacokinetic data and animal safety data (5). Originally, there were only 9 steps in the ascending drug- and light-dose schedule (3 drug doses of 0.25, 0.50, and 0.70 mg/kg and 3 light doses of 50, 100, and 150 J/cm²).

Verteporfin for Injection was supplied in 25 mg vials. To reconstitute, 12 mL of sterile water was added for a total volume of 12.5 mL (i.e., 2 mg/mL) of reconstituted drug. The desired drug concentrations were prepared by further diluting the reconstituted drug in 5% dextrose-water (D5W). Each patient was to receive drug in a total volume of 100 mL. Verteporfin was injected intravenously with an infusion pump at a rate of 1 mL/min for the first 10 minutes and then the infusion rate was increased to 3 mL/min if vital signs were stable until the bag containing verteporfin was emptied (about 35 minutes). The infusion lines were then flushed with D5W at a rate of 3 mL/min to give a total infusion time of 45 minutes.

Therapeutic nonthermal light treatment was applied to the treatment field(s) with an argon-ion pumped-dye laser (APDL) equipped with a QLT direct connect microlens fiber after the initiation of verteporfin infusion. Initially, light was to be applied between 3 and 4 hours after the start of drug administration. Amendment 5 expanded the light application time to be between 1.5 hours and 6 hours.

5.3.2 Identity of Investigational Product

Verteporfin is a semisynthetic derivative of hematoporphyrin. It has a maximum light absorption near 690 nm. One batch of verteporfin (R1186-102) was used in the study.

Verteporfin was supplied by the study sponsor (QLT PhotoTherapeutics Inc., Vancouver, Canada) in clear vials of 25 mg of sterile, lipid-based, freeze-dried powder, and was to be protected from light. Once reconstituted, Verteporfin for Injection was stored in the dark under refrigeration at 2-8°C and injected within 4 hours as it did not contain any antimicrobial preservative.

5.3.3 Assignment to Treatment

The QLT PhotoTherapeutics Inc. Clinical Research Coordinator assigned patients to a given treatment group according to the Drug and Light Dose Schema provided in Appendix D.7.1. Verteporfin doses used ranged from 0.15 to 0.50 mg/kg. Light doses ranging from 25 to 150 J/cm² were delivered between 1.5 and 6 hours post the start of verteporfin administration.

Permission to escalate to the next drug or light dose level was also granted centrally by the QLT PhotoTherapeutics Inc. Clinical Research Coordinator. A minimum of 7 days was required before escalation to a new level of drug. Treatment at the next drug dose level could begin only if peritumoral skin reaction was acceptable, there was no evidence of systemic toxicity, and a full review of laboratory data on all patients at the current dose level had been performed. Patients at the same dose combination could enter concurrently.

5.3.4 Assessment of Treatment Compliance

All drug and light doses were administered under the supervision of study personnel. Compliance with the Protocol was monitored by a representative of QLT PhotoTherapeutics Inc. during visits to the study centers. All treatment and assessment procedures were documented in the Case Report Form (CRF) for each patient. Unique pages of the CRF are included in Appendix D.2.

5.3.5 Prior and Concomitant Treatment

As indicated in the study protocol, patients could receive medications as clinically indicated, except for photosensitizing medications such as tetracyclines, during the first week of the study. Patients undergoing anti-HIV therapies were eligible for concomitant photodynamic therapy. However, patients who were concurrently receiving radiotherapy, immunotherapy, chemotherapy or hormonal therapy were excluded. Patients who had received radiotherapy or chemotherapy within the previous 6 weeks or had received PHOTOFRIN® within the past 12 weeks were also ineligible.

Amendments to the Protocol (September 1991, February 1992, and July 1992) allowed for patients with de novo basal cell carcinoma to receive conventional treatment of their lesions at the discretion of the Investigator. After receiving excision, the patients were not followed for tumor response or local peritumoral skin reaction. However, they were followed for the collection of safety information for at least 3 months following the verteporfin injection.

5.4 Study Procedures

5.4.1 Pretreatment Procedures (-1 Month to -2 Days)

Pretreatment procedures included recording of medical history and demographic information, physical examination, ophthalmological examination, and clinical laboratory tests. Biopsy samples were obtained to confirm patient's eligibility. Baseline skin photosensitivity was determined by exposing nine 1 cm² areas of normal skin on the patient's back to UVA/visible light from a solar simulator. Study procedures used prior to treatment are presented in Table 1.

TABLE 1. Summary of Study Procedures (Pretreatment)

Procedures	Prior to Treatment		
	1 Month	1 Week	2-3 Days
Chest X-ray	X		
History and Physical Examination		X	
Biopsy of Lesion(s)	X		
Ophthalmological Examination ^a	X		
Documentation of Concurrent Medications		X	
Patient and Treatment Assignment			X
Weight		X	
ECG		X	
Laboratory Tests ^b		X	
Broad Spectrum Light Photosensitivity Assessment		X	
Skin Type Assessment		X	

^a For confirmation of eligibility

^b Laboratory tests included: hematology (red blood cell count, reticulocytes, hemoglobin, hematocrit, white blood cell count, neutrophils, lymphocytes, eosinophils, monocytes, basophils, bands, and platelets), serum chemistry (sodium, potassium, chloride, CO₂, glucose, BUN, creatinine, total protein, albumin, calcium, phosphorus, total bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), LDH, alkaline phosphatase, uric acid, cholesterol, and triglycerides), and urinalysis (appearance, specific gravity, pH, glucose, blood, protein, urobilinogen, ketones, and microscopic findings).

5.4.2 Treatment Day Procedures (Day 0)

On the day of treatment, verteporfin was injected intravenously as described in Section 5.3.1. Light from an APDL was applied to the treatment sites after the end of drug infusion. Vital signs were monitored prior to, during, and after drug infusion. Blood samples (7 to 10 mL of blood) were drawn into potassium oxalate/sodium fluoride tubes for the pharmacokinetic study. Urine samples were to be collected at 0 hour, 12 hours, and 24 hours post drug infusion.

TABLE 2. Summary of Study Procedures (Treatment Day)

Procedures	-1 Hour	Time 0	1.5 to 6 Hours
Vital Signs Assessment	X		
ECG			X ^a
Karnofsky Performance Status Rating	X		
Blood Drawn for Pharmacokinetics	X		X ^b
Measurement of Lesions	X		
Drug Infusion		X	
Vital Signs Assessment		X ^c	X ^c
Light Exposure of Lesion (PDT)			X

^a Between 4-6 hours after drug infusion.

^b Blood for pharmacokinetics was collected at various times (see Table 3 in Section 5.5.2).

^c Vital signs were assessed 5 minutes from Time 0 (start of infusion) and then every 10 minutes during infusion and at 30 minutes post infusion, then hourly for 24 hours or until the patient was stable. Respiration rate recording was deleted for patients after February 1992 (Amendment 3). For patients enrolled after July 1992 (Amendment 4), vital signs were only recorded at 30 minutes post-infusion, then hourly for 24 hours or until the last patient was stable.

5.4.3 Posttreatment Procedures (Days 1 to 90)

Posttreatment procedures included monitoring of adverse events, evaluating skin photosensitivity to broad spectrum light and blood sampling for pharmacokinetic analysis. Adverse event definitions and procedures for evaluating photosensitivity of normal skin are provided in Section 5.5.4.1 and Appendix D.6.3 respectively.

Clinical assessment of treatment fields was performed to determine PDT-induced normal skin reactions, tumor response, and patient response. Photographs were taken on Days 1 and 28 post PDT.

5.5 Efficacy, Pharmacokinetic, and Safety Variables

5.5.1 Efficacy Endpoints and Assessments

Efficacy was a secondary objective in this study. The Protocol stipulated that the efficacy endpoint was patient response (p). Patient response was obtained by aggregating the tumor (τ) responses.

5.5.1.1 Tumor Response

The change in tumor size (area) was recorded by measuring the longest diameter and the one perpendicular to it each time and calculating the area. Photographs and documentation of measurements and characteristics of the lesions post treatment were recorded at each evaluation point. Tumor (lesion) assessment post treatment was based on the following definitions:

Complete Response (CR_τ):	no visible sign of tumor
Partial Response (PR_τ):	≥50% reduction in tumor size
Stable Disease (SD_τ):	<50% reduction or increase of ≤25% in tumor size
Progressive Disease (PD_τ):	>25% increase in tumor size

Tumors that remained a CR_τ for at least 1 month were biopsied for histologic examination. This included only tumors that received PDT but no other alternative therapy.

5.5.1.2 Patient Response

The primary efficacy variable in this study was patient response. Patient response was obtained by aggregating tumor (lesion) response(s).

Patient Complete Response (CR_P):	All treated lesions are CR _T
Patient Partial Response (PR_P):	All treated lesions are a combination of CR _T and PR _T or all lesions are PR _T
Patient Stable Disease (SD_P):	Any treated lesion SD _T
Patient Progressive Disease (PD_P):	Any treated lesion PD _T

5.5.2 Pharmacokinetic and/or Pharmacodynamic Assessments

Blood samples from 22 patients were taken for pharmacokinetic assessment. Sampling times are outlined in Table 3.

TABLE 3. Blood Sampling Times for Pharmacokinetic Analysis

Sample	Description	Time
1	Baseline	(Time 0-1 hour)
2	Midway during drug infusion	(Time 0 + ~20 min.)
3	Immediately post end of drug infusion	(Time 0 + ~45 min)
4	15 minutes post end of drug infusion	(Time 0 + ~60 min)
5	30 minutes post end of drug infusion	(Time 0 + ~75 min.)
6	60 minutes post end of drug infusion	(Time 0 + 1 h and 45 min.)
7	90 minutes post end of drug infusion	(Time 0 + 2 h and 15 min.)
8	2 hours post end of drug infusion	(Time 0 + 2 h and 45 min.)
9	3 hours post end of drug infusion	(Time 0 + 3 h and 45 min)
10	4 hours post end of drug infusion	(Time 0 + 4 h and 45 min)
11	6 hours post end of drug infusion	(Time 0 + 6 h and 45 min.)
12	8 hours post end of drug infusion	(Time 0 + 8 h and 45 min.)
13	12 hours post end of drug infusion	(Time 0 + 12 h and 45 min.)
14	24 hours post end of drug infusion	(Time 0 + 24 h and 45 min.)
15	48 hours post end of drug infusion	(Time 0 + 48 h and 45 min.)
16	72 hours post end of drug infusion	(Time 0 + 72 h and 45 min.)
17	96 hours post end of drug infusion	(Time 0 + 96 h and 45 min.)

5.5.3 Safety Assessments

Systemic toxicity of verteporfin was a secondary endpoint. It was assessed clinically by clinical examination and recording of all adverse events on all visits including the treatment day. Biologically, systemic toxicity was determined by blood and urine analyses at Days 1, 2, 3, and 7. While systemic toxicity was evaluated using the NCI common toxicity criteria, this information is more comprehensively collected as adverse events. The report, therefore, focuses on the summary of adverse events.

5.5.3.1 Adverse Events

Adverse events were assessed at treatment and at all follow-up visits. A serious event in this study meant any experience that suggested a significant hazard, contraindication, side effect or precaution associated with the use of verteporfin or of the device. Serious adverse events included, but were not limited to, events that 1) were life-threatening, 2) were permanently or severely disabling, 3) required hospitalization or prolonged hospitalization, 4) resulted in death due to any cause which occurred within 30 days of receiving study medication; and 5) resulted in congenital anomaly, a new cancer or drug overdose.

Causal relationship to the study drug or treatment was evaluated according to the definitions presented in Table 4 below. Associated AEs were defined as those considered to be definitely, probably, or possibly related to therapy. Adverse change in physical signs or symptoms was rated as mild (defined as awareness of sign or symptoms, but easily tolerated), moderate (defined as discomfort enough to cause interference with usual activity) or severe (incapacitating with inability to work or do usual activity). Adverse events were coded by body system using COSTART.

TABLE 4. Adverse Event Causal Relationship Definitions

Causal Relationship	Definition
Definitely	Adverse event experience that: <ul style="list-style-type: none">• follows a reasonable temporal sequence from drug administration or treatment.• abates upon discontinuation of the drug (dechallenge) or treatment.• is confirmed by reappearance of the reaction on repeat exposure (rechallenge).
Probably	Adverse event experience that: <ul style="list-style-type: none">• follows a reasonable temporal sequence from drug administration or treatment.• abates upon discontinuation of the drug (dechallenge) or treatment.• cannot be reasonably explained by the known characteristics of the patient's clinical state.
Possibly	Adverse event experience that: <ul style="list-style-type: none">• follows a reasonable temporal sequence from drug administration or treatment.• could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
Possibly not	Adverse event experience that: <ul style="list-style-type: none">• doesn't follow a reasonable temporal sequence from drug administration or treatment.• could have been produced by the patient's clinical state or by other modes of therapy administered to the patient.
Remotely	Adverse event experience where the temporal association between the experience and the drug or treatment is such that the drug or treatment is not likely to have had any reasonable association with the observed event.
Definitely not	Adverse event experience that is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

5.5.3.2 Laboratory Data

Laboratory tests for safety (see Table 1 footnotes for a list of laboratory studies) were assessed by the Investigator as to their clinical significance. Any posttreatment laboratory value which was found to be clinically significant was then assessed by the Investigator for the causal relationship to the study drug or treatment.

5.5.3.3 Vital Signs

Vital signs (temperature, pulse, respiration, and blood pressure) were taken prior to treatment. Blood pressure, pulse, and respiration were taken at the start of drug infusion, throughout the first 5 minutes, every 10 minutes during infusion and at 30 minutes post drug infusion. Assessment was then continued hourly for 24 hours or until the patient was stable and vital signs were within their normal range. Respiration rate measurement was later abandoned (Amendment 3) as it was judged by the Investigator to be an unreliable parameter for drawing conclusions.

Baseline ECG was recorded within 7 days prior to treatment. On the day of treatment, ECG was taken immediately after drug infusion and at 4 and 24 hours afterwards. To give more time for taking measurement, Amendment 3 modified the 4-hour post infusion ECG to be between 4 and 6 hours post infusion. The 24-hour post infusion ECG was deleted since it did not give any further data of value when compared to the 4-6 hour ECG.

Any abnormalities that were of clinical significance were commented on by the Investigator in the Case Report Form.

5.5.3.4 Other Safety Variables

a) Duration of Photosensitivity of Normal Skin

Normal Skin Photosensitivity Testing Procedures: Appendix D.6.3

Duration of photosensitivity of normal skin was considered as the primary endpoint in the Protocol. Photosensitivity of normal skin independent of therapeutic light treatment was assessed on each patient's back using a solar simulator. The baseline reading was recorded between 1 month and 1 week prior to drug infusion. The method used for determining photosensitivity of normal skin is presented in Appendix D.6.3.

The duration of skin photosensitivity due to verteporfin infusion was evaluated 24 hours post-drug administration and daily thereafter until no reaction was visible by exposing defined areas of each patient's back to light from the solar simulator. The

range of doses from the solar simulator was based on each patient's initial MED assessment. The highest light dose used was 215 J/cm². Evaluations included photographs, documentation, and grading.

b) Peritumoral PDT Skin Reaction

Skin Toxicity Scale: Appendix D.5.2

Peritumoral (local "normal" skin within the treatment field) skin reaction to a therapeutic drug-light dose combination was assessed after PDT. The treatment site was photographed, the reaction was documented and evaluated according to the Skin Toxicity Scale (Appendix D.5.2). Initially, assessments were to be made at 24 hours from the time of drug and light treatment (Day 1) and at Days 2, 3, 4, 5, 6, 7, 14, 21, 28, and 35 posttreatment, and at 2 and 3 months or until no reaction was visible. Amendment 3 abolished assessments required on Days 4, 5, 6, and 35. Photographs of the treatment sites were to be obtained on visits of Day 1 and Day 28.

5.6 Data Quality Assurance

The use of standard terminology and the collection of accurate data was ensured by regular monitoring visits. During these visits the monitor reviewed the compliance with the Protocol, the consent procedure, completion of case report forms, the adverse event procedure and verification of data. Key items of data transcribed onto the case report forms, such as treatment dates and laboratory safety test results, were checked against source documents in the presence of the Investigator or his/her delegates, and any inconsistencies resolved. Clinical site inventory was controlled by using the Investigational Drug Accountability Record Form and the Clinical Trial Fiber Inventory Form.

5.7 Statistical Methods

5.7.1 Sample Size

Based on 9 different drug- and light-dose combinations and anticipated enrollment of at least 3 patients per each regimen, the anticipated number of patients was between 27 and 45 patients.

5.7.2 Statistical Analysis Plan

5.7.2.1 Analysis of Efficacy

The efficacy objective of this study was the estimation of the presence of a therapeutic effect of verteporfin and light. Patient response was to be evaluated by clinical assessment of change in tumor size. A drug and light dose combination was considered effective if a 20% complete or partial response was obtained. No actual statistical analysis plan was specified in the Protocol (see Section 5.8.2 for details on analysis performed).

5.7.2.2 Analysis of Pharmacokinetics

A statistical plan was not provided in the Protocol (see Section 5.8.2 for details on analysis performed).

5.7.2.3 Analysis of Safety Variables

NCI Common Toxicity Criteria: Appendix D.5.1

The Protocol planned to estimate a maximum tolerated dose (MTD) as the highest drug-light combination that could be safely administered to patients without causing a treatment related Grade 2 or higher systemic toxicity (based on the NCI Common Toxicity Criteria – see Appendix D.5.1) and/or a Grade 3 or higher PDT-induced skin reaction in the peritumoral area within the treatment field using the skin toxicity scale (Appendix D.5.2).

The standard procedure used in chemotherapeutic agents was adopted in the Protocol for the estimation of MTD. Drug and light dose escalation continued on a proportionate scale and were halved in the presence of toxicity. When toxicity is encountered at any of the evaluation times after the increase of one modality (light or drug) the other modality is decreased.

Analytical plans for adverse events, laboratory variables or other safety parameters were not provided in the Protocol (see Section 5.8.2 for details on analysis performed).

5.8 Study Modifications

Protocol Amendments: Appendix D.1

5.8.1 Protocol Amendments

The Protocol for this study was amended on four different occasions as outlined in Table 5.

TABLE 5. Summary of Amendments to Study BPD 001

Amendment	Date	Subject	Number of Patients^a Enrolled
Original Protocol	May 1991		
1	July 1991	<ul style="list-style-type: none"> • PK sampling • Adverse event reporting 	0
2	September 1991	<ul style="list-style-type: none"> • Inclusion/Exclusion criteria • Dose escalation rules 	0
3	February 1992	<ul style="list-style-type: none"> • Inclusion/Exclusion criteria • Description of procedures • Use of solar simulator 	6
4	July 1992	<ul style="list-style-type: none"> • Inclusion/Exclusion criteria • Photosensitivity testing procedure • PK sampling 	13
5	June 1993	<ul style="list-style-type: none"> • Inclusion criteria • Light delivery time • Biopsy sampling 	25

^a Number of patients already enrolled into the study at the date of the amendment.

The first and second amendments, preceded the enrollment of any patients. Amendment 1 involved QLT personnel change, rewording of instructions for reporting adverse events and the use of potassium oxalate/sodium fluoride tubes for collecting blood samples.

Amendment 2 broadened the eligibility criteria by allowing BCC patients with symptomatic de novo tumors outside the treatment fields to be included. These de novo lesions could be removed by surgical excision one week after PDT treatment or at the Investigator's discretion. Excision could be delayed up to four weeks after PDT if the Investigator judged it to be necessary. It further specified that tumor and peritumoral area evaluations would continue in these patients until surgical excision. Thereafter, patients would return for safety evaluation only for up to 3 months.

Amendment 2 also redefined the dose escalation rule for the study, specifying that the first two patients for each dose escalation step did not need to be patients with metastatic cancer. At any given dose combination patients could be entered concurrently. Recommended period for eye protection from strong light was modified from several months to at least 3 months.

Amendment 3, in February 1992, following the enrollment of 6 patients, extended the inclusion criteria to include Kaposi's sarcoma patients undergoing anti-HIV therapies. The exclusion criteria was amended to exclude patients with invasive SCC, serious ophthalmic disease and unstable cardiovascular disease. Vital signs would not include respiration rate because, based on Investigator experience, this was not a reliable parameter to draw conclusion on. Time to obtain confirmatory biopsy sample was changed from within 1 month prior to verteporfin infusion to within 1 week. The 24-hour post infusion ECG was deemed unnecessary. Only one

ECG taken between 4-6 hours was required. Time before excision of de novo BCC was extended from 4 to 8 weeks after PDT. Number of follow-up visits was reduced from weekly after PDT to only Days 1, 2, 3, and 7 posttreatment. The visit on 35 ± 2 days was cancelled.

The drug and light dose escalation rule was changed to allow a minimum of 7 days after last patient treatment between enrollment. Amendment 3 also added that, if a generalized skin toxicity or an unacceptable systemic toxicity reaction of a nature related to the treatment which was a Grade 2 or higher on the NCI Common Toxicity Criteria occurred, at any time, the dosing schedule would be reevaluated and amended before resuming patient enrollment. The methodology for photosensitivity testing was altered.

Amendment 4, in July 1992, following the enrollment of 13 patients, excluded patients with a history of diffuse liver disease and/or abnormal liver function tests at baseline. Since PK data was available from 8 patients receiving 0.25 mg/kg of verteporfin, the amendment specified that no further PK sampling would be done at this drug dose. Because of the occurrence of Grade-4 local peritumoral PDT-induced skin reactions in Patients 10, 11, 12, and 13, who had received 0.50 mg/kg or 0.375 mg/kg of verteporfin, the amendment suggested that the drug dose not be further increased, but be kept at 0.25 mg/kg and increase the light dose to 150 J/cm^2 for the next patient. The amendment called to delete further UVB testing, as it had provided no valuable information.

Amendment 5 in June 1993, following the enrollment of 25 patients allowed the inclusion of outpatients. It also permits the inclusion of de novo basal cell carcinoma patients with symptomatic lesions outside the treatment fields. The light treatment time was expanded from 3-4 hours post drug infusion to 1.5-6 hours, and more than one light dose could be used on a patient. The amendment also allowed punch biopsy of CR tumors at 3 months.

Further details of the specific changes for each amendment made can be found in Appendix D.1.

5.8.2 Other Changes in the Conduct of the Study or Planned Analysis

5.8.2.1 Changes in the Conduct of the Study

Multiple treatments were not stipulated in the Protocol or its amendments. However, four patients (9, 20, 23, and 30) received more than one course of PDT.

5.8.2.2 Analysis of Efficacy

The original Protocol did not provide an analytical plan for efficacy.

For the report, analysis of efficacy was based on the maximum tumor response at any time point for evaluation up to and including 3 months. Complete tumor response rates were analyzed in terms of tumor type (i.e., primary versus metastatic skin cancer), drug dose, light dose and time of final assessment after treatment (up to 90 days) by logistic regressions, using the lesion as the experimental unit. A $p \leq 0.05$ value (2-sided) was used.

Treatment interval between courses for these patients was at least 3 months. For the report, each tumor presented in these patients was considered as an experimental unit irrespective of treatment course.

5.8.2.3 Analysis of Pharmacokinetics

The original Protocol did not provide a plan for pharmacokinetic analyses.

For the report, the correlation between the dose and pharmacokinetic parameters descriptive of the extent of exposure and the maximal plasma concentrations was assessed using linear regression analysis (Proc Reg and SAS).

The AUC_{0-24} was calculated by the trapezoidal rule and the AUC_{inf} was calculated as follows:

$$AUC_{0-inf} = AUC_{0-24} + C_1 / K_{el}$$

where C_1 is the last measurable concentration of the analyte, and K_{el} the apparent elimination rate constant.

Maximum plasma concentration (C_{max}) was determined by visual inspection of the data. The total clearance (CL) was calculated using the equation:

$$CL = (\text{Dose} * 0.5^a) / AUC_{0-inf}$$

^a This 0.5 factor is not used for CL calculation for verteporfin (sum)

The volume of distribution at steady state (V_{ss}) was calculated using the equation:

$$V_{ss} = CL * MRT$$

Where MRT is mean residence time using the following equation:

$$MRT = AUMC_{0-inf} / AUC_{0-inf} - \text{Mean Absorption Time (MAT)}$$

$$MAT = [(10/2)*0.1 + (35/2)*0.9] / 60$$

AUMC is area under the first moment curve extrapolated to infinity.

Compartmental analysis was used to derive parameters to describe the distribution and disposition kinetics of BPD-MA_C and BPD-MA_P. A two-compartment model was found to best fit the observed data. All plasma profiles were fitted by this model except one patient for BPD-MA_C. The distribution rate constant (alpha), the elimination rate constant (beta) and their corresponding half-lives were calculated. The NLIN procedure of SAS was used for this purpose. The following differential equation was used:

$$C_p = Ae^{(-\alpha \cdot t)} + Be^{(-\beta \cdot t)}$$

Where A and B are the y-intercepts of the distribution exponential and the elimination exponential, respectively, A weighing of $1/c^2$ was used for the plasma concentrations of the two analytes, to improve the quality of fitting.

5.8.2.4 Analysis of Safety Variables

a) Adverse Events

Analytical plans were not specified in the Protocol for safety evaluation. For the report, systemic toxicity and safety of verteporfin was tabulated overall and by body system. Adverse events were displayed, using COSTART, as actual number of occurrences and as percentage of patients. These include all adverse events observed by the Investigators or reported by the patients at all visits.

b) Laboratory Variables

Comparisons within group changes between baseline and visit Days 1, 2, 3, and 7, and optional retreatment were made. A 2x2 square shift was made for every variable to summarize the distribution of patients who were below normal, normal or above normal. McNemar's Chi-square (PROC FREQ) for matched pairs was used to test a significant shift in the distribution of value from baseline.

c) Special Safety Issues

i) Duration of Photosensitivity of Normal Skin

A statistical analysis plan was not provided in the Protocol. For the report, the duration of normal skin photosensitivity testing was analyzed in two ways. First, the duration of measurable UVA/Vis photosensitivity was determined among different drug dose groups using descriptive statistics. In the second analysis, the relationship between the measured photosensitivity (i.e., 1/MED, transformed logarithmically for curve fitting

purposes) on a given day after verteporfin administration was also evaluated by regression analysis to assess the rate of photosensitivity reduction over time.

ii) **Peritumoral Skin Reactions**

A procedure to analyze peritumoral skin reaction was not specified in the Protocol. In the report, peritumoral skin reaction occurring at each drug and light dose combination was analyzed using descriptive statistics. Skin reactions, according to severity, were displayed as actual number and as percentage.

6. STUDY PATIENTS: DISPOSITION AND DEMOGRAPHY

6.1 Disposition of Patients

Thirty-five patients were treated for a total of 40 courses of PDT in this study. Three of these patients received 2 courses of therapy, and one of these patients received 3 courses of therapy. Treatment interval between courses for these patients was at least 3 months. A total of 8 patients did not complete the 3-month follow-up visit. Table 6 summarizes the patients in each drug-light dose combination and provides reasons for patients not completing the study.

TABLE 6. Patient Assignment by Drug and Light Dose

Course of Therapy	Verteporfin (mg/kg)	Light Dose (J/cm ²) ^a	Number of Patients		
			Treated	Completed ^b	Withdrawn ^c
1	0.15	150	2	2	
		75/125	1	1	
	0.25	150	8	6	1 ^d , 1 ^e
		50	3	1	1 ^d , 1 ^f
		100	5	4	1 ^e
		150	2	2	
	0.30	25/50	3	2	1 ^d
		50	1	1	
		50/75	5	5	
	0.375	50	2	1	1 ^e
50		3	2	1 ^d	
2	0.15	150	1	1	
		25	1	1	
	50/75	2	2		
3	0.30	50/75	1	1	

^a Thirteen patients received 1 drug dose but had two light doses at different treatment fields

^b Patients had their 3-month assessment

^c Patients did not have their 3-month assessment

^d Due to death

^e Due to tumor progression, patient received alternative systemic therapy

^f Receive another course of PDT under single patient exemption before the end of the 3-month follow-up period

Four patients (3, 11, 18, and 29) died during the study period, three due to progressive metastatic diseases and one as a result of progressive liver disease. Detailed descriptions of these patients are presented in Section 9.3.

Three patients (5, 13, and 16) did not complete the 3-month visit due to progression of their skin tumors. These patients received alternative systemic therapy as allowed in the Protocol.

One patient (2) withdrew 89 days after receiving her first course of PDT in order to have a second PDT course for her new tumors under single patient exemption. Approvals from the

IRB and FDA were obtained before the second treatment. Tumors treated in the first course were not followed after Day 89.

6.2 Data Set Analyzed

Data from all enrolled patients was used in the analysis of both safety and efficacy.

6.3 Demographic and Other Baseline Characteristics

Demographic and Baseline Data Listings: Appendix E.1

Table 7 provides information regarding the tumor types treated in this study. By-patient tabular listings of individual patient demographic and baseline data are presented in Appendix E.1.

TABLE 7. Patient Demographics and Tumor Types

Characteristic	n=35
AGE (years)	23-80
Mean (years)	59
GENDER	
Male	17
Female	18
TUMOR TYPES	n=20
Primary nonmelanoma skin cancer	
Sporadic BCC	10
Nevoid BCC syndrome	9
Bowen's disease (SCC in situ)	1
Tumors metastatic to skin	n=15
Breast	7
Gastrointestinal	2
Metastatic amelanotic melanoma	2
Lung	1
Cutaneous angiosarcoma	1
Uterine cervix	1
Metastatic cutaneous SCC	1

7. PROTOCOL DEVIATIONS

7.1 Protocol Deviations that Led to Exclusion from the Analysis

No patients were excluded from the efficacy and safety analyses due to protocol deviations. The Protocol required collection of 2 urine samples from each patient at 0-12 hours and 12-24 hours for pharmacokinetic analysis. No analysis of verteporfin in urine was performed due to the insensitivity of the assay for urine samples. Similarly, analysis of verteporfin in plasma was not performed on samples collected after 24 hours.

7.2 Protocol Deviations that did not Lead to Exclusion from the Analysis

Initially, each patient was to receive only one drug and light dose combination. As the study progressed, some patients were given one drug dose but were exposed to two light doses at different treatment fields (Amendment 5, June 1993). This made the analysis of patient response rate in these patients not as meaningful. A total of 13 patients had treatment fields exposed to 2 different light doses.

Four patients (9, 20, 23, and 30) received more than one course of PDT. Multiple treatments were not stipulated in the Protocol or its amendments. Treatment interval between courses for these patients was at least 3 months. For the report, each tumor presented in these patients was considered an experimental unit irrespective of treatment course.

For the normal skin photosensitivity measurement, photosensitivity testing was accomplished using an Oriel broad light spectrum solar simulator. Patients were to expose nine 1 cm² areas of normal skin on the back to various doses of broad spectrum light. The light dose that produced a minimal erythema reaction with clearly defined borders was considered as the minimal erythematous dose (MED). Patients were to be retested daily after verteporfin administration to determine the number of days it would require for the MED to return to baseline value. When the study was conducted, it was discovered that all patients had a MED in excess of 215 J/cm². Hence, 215 J/cm² was considered as the baseline MED for all patients.

The Protocol inclusion criteria specified that tumors had to be at least 0.5 cm in two perpendicular diversions to be treated by PDT. The study included 16/104 of the primary and 6/78 of the metastatic lesions treated that were less than 0.5 cm in both linear dimensions. Those lesions were included in the intent-to-treat efficacy analyses.

8. EFFICACY AND PHARMACOKINETIC RESULTS

8.1 Efficacy Results

Listing of Tumor Response: Appendix E.2.1

Listing of Patient Response: Appendix E.2.2

Listing of Biopsy Results for Complete Responded Tumors: Appendix E.2.3

As a first-time test of the drug in humans, Study BPD 001 was not primarily designed to be an efficacy study. Efficacy is a secondary endpoint, and the Protocol stipulated that efficacy evaluation would be based on patient response. Patient response was to be obtained by aggregating tumor (lesion) responses.

As the study was executed, it became less meaningful to report efficacy in terms of patient response for each drug-light combination, since some patients received different light doses on different treatment fields. Therefore, most analyses have been done at the tumor level which is consistent with most literature reports on primary skin tumors. The analyses stratified tumors into two groups – primary tumors and metastatic tumors. Tumor response was recorded as a complete tumor response (CR_T) when no tumor was clinically visible. A partial tumor response (PR_T) was defined as tumors which reduced in size by 50% or more. For the analysis, each tumor was considered as an experimental unit, which is consistent with other reported trials in the treatment of skin cancer.

8.1.1 Efficacy Results of Patients with Primary Tumors

Twenty patients with 104 primary lesions (103 basal cell carcinoma and 1 squamous cell carcinoma in situ) were treated by PDT. Tumor response rates were assessed by evaluating the best clinical response achieved at any one of the follow-up visits (Table 8). A listing of individual tumor response is presented in Appendix E.2.1.

TABLE 8. Primary Tumor Response by Drug and Light Dose

Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Lesions Treated	Number (%) of Tumors			
			Complete Response (CR _T)		Partial Response (PR _T)	
			Any Assessment	Last Visit	Any Assessment	Last Visit
0.15	150	3	1 (33)	0 (0)	2 (67)	1 (33)
0.20	75	3	3 (100)	3 (100)	0 (0)	0 (0)
	125	2	2 (100)	2 (100)	0 (0)	0 (0)
	150	16	16 (100)	16 (100)	0 (0)	0 (0)
0.25	50	7	0 (0)	0 (0)	1 (14)	1 (14)
	100	10	7 (70)	7 (70)	2 (20)	1 (10)
0.30	25	2	2 (100)	2 (100)	0 (0)	0 (0)
	50	40	38 (95)	38 (95)	0 (0)	0 (0)
	75	11	7 (64)	7 (64)	2 (18)	1 (9)
0.375	50	3	3 (100)	3 (100)	0 (0)	0 (0)
0.50	50	7	7 (100)	7 (100)	0 (0)	0 (0)
TOTAL		104	86 (83)	85 (82)	7 (7)	4 (4)
[95% CI on CR _T or PR _T rate]			[75 - 90]	[74 - 89]	[2 - 12]	[0 - 8]
Any Assessment: CR _T +PR _T rate [95% CI on CR _T + PR _T rate]					89 [84 - 95]	
Last Visit: CR _T +PR _T rate [95% CI on CR _T + PR _T rate]					86 [79 - 92]	

A complete clinical tumor response (CR_T) was observed in 83% (86/104) of primary tumors at any visit and 82% (85/104) of primary lesions at last visit. Partial clinical response was achieved in 7% (7/104) of the tumors at any assessment and 4% (4/104) at the last visit. Biopsy samples were obtained from 28 CR_T sites. Of these biopsied samples, 75% (21/28) were proven tumor-free histologically. Listings of patient response and biopsy results are provided in Appendices E.2.2 and E.2.3.

Table 9 displays the patient response information for the 20 treated patients with primary tumors.

TABLE 9. Patient Response Rate of Patients with Primary Tumors

Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Patients	Number (%) of Patients						
			Complete Response (CR _P)			Partial Response (PR _P)			
			Any Assessment	Last Visit		Any Assessment	Last Visit		
0.15	150	1	0 (0)	0 (0)		1 (100)	0 (0)		
0.20	75/150	6	6 (100)	6 (100)		0 (0)	0 (0)		
0.25	50/100	5	2 (40)	2 (40)		0 (0)	0 (0)		
0.30	25/75	5	4 (80)	4 (80)		0 (0)	0 (0)		
0.375	50	1	1 (100)	1 (100)		0 (0)	0 (0)		
0.50	50	2	2 (100)	2 (100)		0 (0)	0 (0)		
TOTAL		20	15 (75)	15 (75)		1 (5)	0 (0)		
[95% CI on CR _P or PR _P rate]			[56 - 94]	[56 - 94]		[0 - 15]	[0 - 0]		
Any Assessment: CR _P +PR _P rate [95% CI on CR _P + PR _P rate]						80 [62 - 98]			
Last Visit: CR _P +PR _P rate [95% CI on CR _P + PR _P rate]						75 [56 - 94]			

When examining the patient response rate for the first course of PDT, 75% (15/20) of patients had a CR_P at any visit and at their last assessment. Five percent (1/20) had a PR_P at any assessment and none at the last visit. Thus, combining CR_P and PR_P, 75% (15/20) of patients had responded by their last visit with a 95% confidence interval between 56 and 94%.

8.1.2 Efficacy Results of Patients with Metastatic Tumors

Fifteen patients were treated for metastatic disease involving a total of 78 tumors. The best clinical tumor responses during any assessment visit are provided in Table 10, and a listing of individual tumor response is provided in Appendix E.2.1.

TABLE 10. Metastatic Tumor Response by Drug and Light Dose

Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Lesions Treated	Number (%) of Tumors			
			Complete Response (CR _T)		Partial Response (PR _T)	
			Any Assessment	Last Visit	Any Assessment	Last Visit
0.15	150	13	5 (38)	5 (38)	7 (54)	1 (8)
0.20	150	13	6 (46)	4 (31)	5 (38)	4 (31)
0.25	50	12	3 (25)	1 (8)	0 (0)	0 (0)
	100	6	2 (33)	0 (0)	3 (50)	0 (0)
	150	5	2 (40)	2 (40)	3 (60)	3 (60)
0.30	25	9	5 (56)	4 (44)	3 (33)	0 (0)
	50	9	8 (89)	5 (56)	1 (11)	0 (0)
	75	2	2 (100)	2 (100)	0 (0)	0 (0)
0.375	50	4	4 (100)	4 (100)	0 (0)	0 (0)
0.50	50	5	5 (100)	5 (100)	0 (0)	0 (0)
TOTAL		78	42 (54)	32 (41)	22 (28)	8 (10)
[95% CI on CR _T or PR _T rate]			[43 - 65]	[30 - 52]	[18 - 38]	[4 - 17]
Any Assessment: CR _T +PR _T rate [95% CI on CR _T + PR _T rate]					82 [74 - 91]	
Last Visit: CR _T +PR _T rate [95% CI on CR _T + PR _T rate]					51 [40 - 62]	

For all doses combined, a complete clinical tumor response (CR_T) was observed in 54% (42/78) of metastatic lesions at any visit and 41% (32/78) of lesions at last visit. Partial clinical responses were achieved in 28% (22/78) of tumors at any assessment and 10% (8/78) at the last visit. Only 2 CR_T metastatic tumors were biopsied, and residual malignant cells were found in both samples histologically. Listing of patient response and biopsy results are provided in Appendices E.2.2 and E.2.3.

Response by patient for metastatic lesions is presented in Table 11.

TABLE 11. Patient Response Rate in Patients with Metastatic Tumors

Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Patients	Number (%) of Patients							
			Complete Response (CR _P)				Partial Response (PR _P)			
			Any Assessment		Last Visit		Any Assessment		Last Visit	
0.15	150	1	1	(100)	1	(100)	0	(0)	0	(0)
0.20	150	3	1	(33)	1	(33)	1	(33)	1	(33)
0.25	50/150	5	1	(20)	1	(20)	1	(20)	1	(20)
0.30	25/75	4	2	(50)	0	(0)	1	(25)	0	(0)
0.375	50	1	1	(100)	1	(100)	0	(0)	0	(0)
0.50	50	1	1	(100)	1	(100)	0	(0)	0	(0)
TOTAL		15	7	(47)	5	(33)	3	(20)	2	(13)
[95% CI on CR _P or PR _P rate]			[21 - 72]		[9 - 57]		[0 - 40]		[0 - 31]	
Any Assessment: CR _P +PR _P rate [95% CI on CR _P + PR _P rate]			67 [43 - 91]							
Last Visit: CR _P +PR _P rate [95% CI on CR _P + PR _P rate]			47 [21 - 72]							

When examining the patient response rate for the first course of PDT, 47% (7/15) were observed to have a CR_P at any assessment and 33% (5/15) maintained the CR_P at their last visit (Table 11). Twenty percent (3/15) had a PR_P at any assessment and 13% (2/15) at their last visit. The combined CR_P + PR_P rate at last visit for metastatic patients was 47% (7/15) with a confidence interval of 21-72%.

8.1.3 Other Exploratory Analyses of Efficacy

SAS Output on Logistic Regression Analysis: Appendix B.1

Except for the patient response rate, the Protocol did not specify other efficacy endpoints. However, further exploratory analyses were performed and are presented in this report to provide additional information and to aid in the selection of doses for subsequent studies.

Tumor response following PDT is a function of both the verteporfin and light doses. SAS outputs on logistic regression analysis are presented in Appendix B.1.

Logistic regression was performed to evaluate the relationship between CR_T and a set of exploratory variables (e.g. drug and light dose and tumor types). Contour graphs showing the drug- and light-dose combinations for achieving a CR_T at 3 months were generated (see Figures 1 and 2).

Figure 1 displays the contour graph resulting from the logistic regression analysis of the primary tumor response.

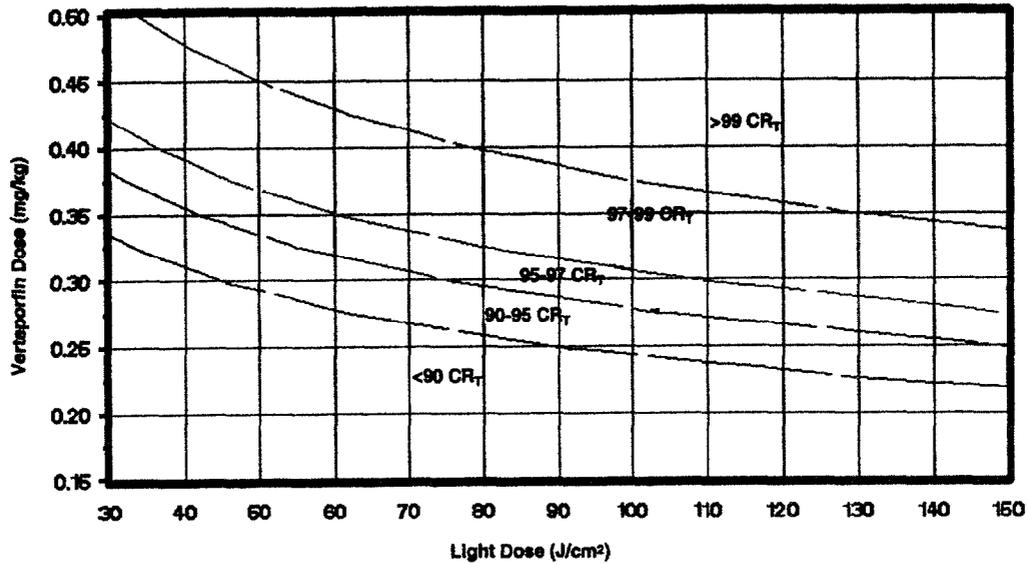


FIGURE 1. Logistic Regression Contour Graph Showing Probability of CR_T % for Primary Tumors

Figure 2 displays the contour graph resulting from the logistic regression analysis of the metastatic tumor response.

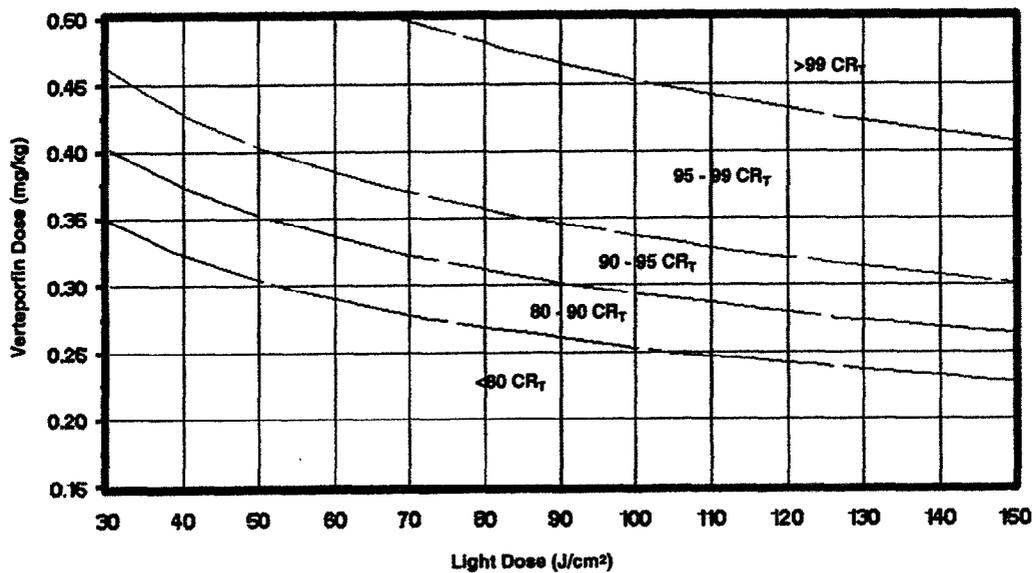


FIGURE 2. Logistic Regression Contour Graph Showing Probability of CR_T % for Metastatic Tumors

Based on the logistic regression contour graphs, for example, in order to achieve a 99% CR_T rate for primary tumors at 3 months, a verteporfin dose of 0.375 mg/kg and a laser light dose of 100 J/cm² is required. Whereas, the same drug and light dose combination could only achieve approximately a 96% CR_T in metastatic tumors.

8.2 Pharmacokinetic Results

Summary of Pharmacokinetic Results for Regioisomer BPD-MA_C: Appendix A.1

Summary of Pharmacokinetic Results for Regioisomer BPD-MA_D: Appendix A.2

SAS Output on Pharmacokinetic Analysis: Appendix B.3

PK Parameters Data Listings: Appendix E.3

Pharmacokinetic data are available for 21 patients who received single intravenous drug doses of 0.15, 0.20, 0.25, 0.375 or 0.50 mg/kg. Of the 21 patients who provided plasma samples for pharmacokinetic analysis, one patient provided two sets of samples after receiving two different doses (0.50 and 0.15 mg/kg) more than a year apart. Her patient number was 9 for the first dose (0.50 mg/kg) and 25 for the second dose (0.15 mg/kg). Therefore, 22 sets of plasma samples are included in the analyses.

Plasma was collected and assayed for the two regioisomers of verteporfin, BPD-MA_C (CL 315,555) and BPD-MA_D (CL 315,585). The results were used to determine the pharmacokinetic parameters of the two analytes and their sum. The data for the sum is presented in Figures 3 and 4 below. Data for each of the regioisomers and the individual pharmacokinetic data, including the plasma concentrations of each regioisomer and their sum at each sampling time point, derived pharmacokinetic variables and the points used to estimate the elimination rate constants are presented in Appendices A.1 and A.2. Listing of individual pharmacokinetic results is provided in Appendix E.3. Data past the 24.75 hour sampling time was below the quantifiable level in all patients except for one single value. Consequently, this data is not included in the pharmacokinetic calculations or in the Appendix E.3.

8.2.1 Noncompartmental Analysis of Verteporfin (Sum of BPD-MA_C and BPD-MA_D)

Figures 3 and 4 present the mean plasma concentration of verteporfin at each sampling time both under linear and semi-log scales.

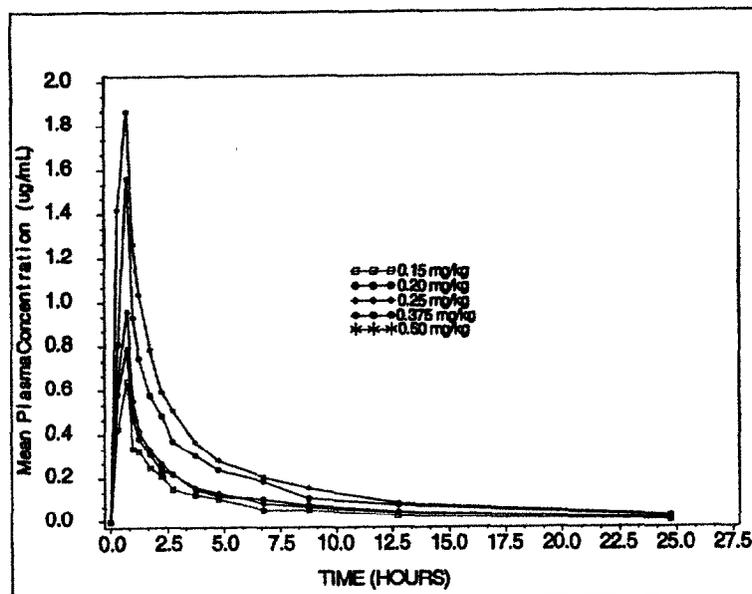


FIGURE 3. Plasma Concentration versus Time Profiles of Verteporfin Following a 45-minute IV Infusion (linear scale)

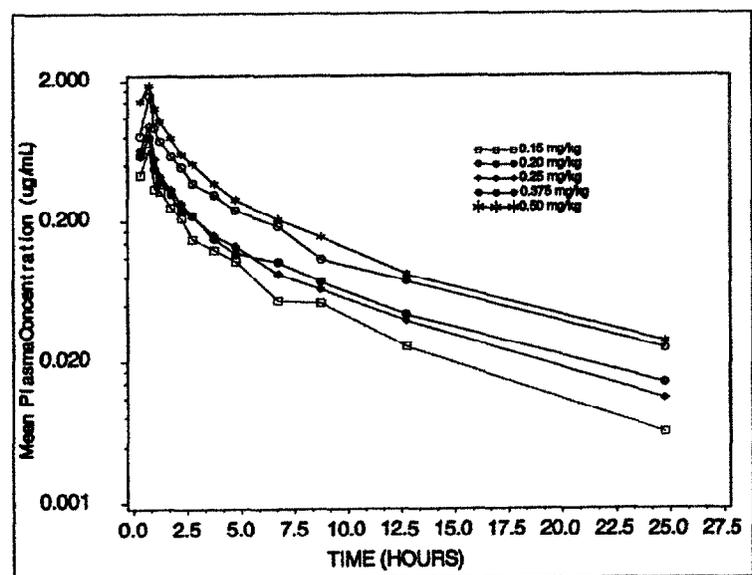


FIGURE 4. Plasma Concentration versus Time Profiles of Verteporfin Following a 45-minute IV Infusion (semi-log scale)

The mean derived pharmacokinetic data for verteporfin is summarized in Table 12.

TABLE 12. Mean Pharmacokinetic Data for Verteporfin

No. of Patients	Drug Dose (mg/kg)	C_{max}		AUC_{0-24}		AUC_{0-12}		$T_{1/2}$		V_{ss}		CL	
		(μ g/mL)	SD	(μ g/hr/mL)	SD	(μ g/hr/mL)	SD	(hr)	SD	(L/kg)	SD	(mL/hr/kg)	SD
2 ^a	0.15	0.68	0.24	1.81	0.71	2.27	0.13	5.46	0.51	0.35	0.00	66.26	3.90
6	0.20	0.79	0.14	2.40	0.59	2.51	0.66	5.79	1.00	0.51	0.14	85.40	27.0
8	0.25	0.97	0.09	2.38	0.55	2.49	0.60	5.12	1.31	0.52	0.03	105.8	26.3
2	0.38	1.56	0.04	4.26	0.40	4.48	0.49	6.25	0.77	0.53	0.03	84.16	9.25
3	0.50	1.87	0.47	5.53	1.28	5.77	1.39	5.94	0.23	0.50	0.11	90.14	21.6

^a For C_{max} and AUC_{0-24} , No. of Patients = 3.

Verteporfin exhibits very similar disposition characteristics among the range of doses studied. The mean apparent elimination half-life ranges from 5.12 hours to 6.25 hours, without definite trend as a function of the dose. Likewise, the volume of distribution (V_{ss}), is approximately 0.5 L/kg for all doses (except for the lowest dose of 0.15 mg/kg, with V_{ss} =0.35 L/kg), indicating that verteporfin is apparently distributed in total body water. The total body clearance (CL) is relatively constant within the range of doses studied, suggesting the absence of dose-dependent kinetics. Exposure is proportional to the administered dose, as depicted by the C_{max} and the AUC parameters. The proportionality is more evident with C_{max} than with AUCs. In the latter case, the mean parameter values do not vary between the 0.20 and 0.25 mg/kg doses, resuming dose proportional increases at higher doses. Correlation analysis of the C_{max} and AUC parameters confirms the linearity of dose-parameter relation (r^2 of 0.815, $p<0.001$, and 0.757, $p<0.001$, respectively).

The above observations strongly suggest that verteporfin kinetics are highly predictable, at least within the range of doses studied and using a 45-minute infusion.

8.2.2 Non-Compartmental Analysis of Regioisomer BPD-MA_C

The mean plasma concentration for BPD-MA_C at each sampling time is presented in Appendix A.1. BPD-MA_C exhibits very similar distribution and disposition kinetics within the range of doses studied. Its apparent half-life is approximately 6.5 hours, its volume of distribution is 0.6 L/kg and the clearance is relatively constant among doses. Dose proportionality is observed for the parameters describing the extent and rate of exposure. The AUC parameter shows a small deviation to linearity in the 0.20 to 0.25 mg/kg dose range. In summary, the pharmacokinetics of BPD-MA_C in the dose range studied are dose independent, and there is no evidence of disposition saturation.

8.2.3 Non-Compartmental Analysis of Regioisomer BPD-MA_D

The mean plasma concentration for BPD-MA_D at each sampling time is presented in Appendix A.2. Behaving similarly to BPD-MA_C, the regioisomer BPD-MA_D shows similarity among doses studied for the distribution and disposition parameters. The elimination half-life presents an average of 5 hours, except for the lowest dose where it is only 3.61 hours. This may be explained by the shorter period of time during which plasma levels were measurable for this dose. The clearance was unchanged across dose levels and the volume of distribution was, on average, 0.44 L/kg for all doses except the lowest, for the reasons mentioned above for the half-life. This volume distribution is lower than that observed for BPD-MA_C. This is due to the higher initial plasma concentrations of BPD-MA_D. The C_{max} exhibits a linear ($r^2=0.799$, $p<0.001$) and proportional increase with the dose. For AUCs, the linear dose-parameter value relationship is similar ($r^2=0.797$, $p<0.001$), with almost no change between the 0.20 and 0.25 mg/kg doses. In summary, the pharmacokinetics of BPD-MA_D in the dose range studied are dose independent and there is no evidence of disposition saturation.

8.2.4 Comparison of the Non-Compartmental Analysis of BPD-MA_C and BPD-MA_D

Comparison of the two regioisomers reveal that their initial maximal plasma concentration differs; the BPD-MA_C regioisomer being consistently lower than the BPD-MA_D counterpart. This was expected as animal pharmacokinetics showed the same trend(s).

It is hypothesized that the initial plasma disposition regioisomer BPD-MA_C is faster than for the BPD-MA_D counterpart. Once this initial difference is over, the two regioisomers exhibit some similarity for the extent of exposure (AUCs) but the distribution and disposition kinetics differ slightly, with the exception of total body clearance which is virtually the same among the two regioisomers. This is mainly due to the time course of the plasma concentrations, for regioisomer BPD-MA_D, the initial concentrations are higher but the distribution and elimination are apparently faster, resulting in a lower $AUMC_{0-tf}$, than for regioisomer BPD-MA_C. Consequently, the V_{ss} reflects that AUMC difference. It is likely that there is no true difference between the two regioisomers in regards to their distribution kinetics. Mean derived pharmacokinetics summary figures and tables for the two regioisomers are presented in Appendices A.1 and A.2.

8.2.5 Compartmental Analysis of BPD-MA_C and BPD-MA_D

Using procedure NLIN of SAS, the plasma concentration versus time profile of BPD-MA_C is best described by a two-compartment model with intravenous administration in and elimination from the central compartment. All patients were successfully fitted to this pharmacokinetic model except Patient 24 (at a dose equal to 0.15 mg/kg), for which goodness of fit was

inadequate in the β portion of the model. No valid parameter estimates could be calculated for this patient.

At all doses investigated, the maximal plasma concentration is generally observed at the end of the infusion and followed by a rapid decrease of the plasma concentration (alpha half-life ranging from 0.25 to 0.57 hours). At approximately 2-3 hours, there is an inflexion of the plasma concentration curve (see Appendix A.1). Thereafter, the disposition of BPD-MA_C has an apparent beta half-life of 5.33 to 6.32 hours, independent of the dose (Appendix A.1). There is a good consistency between the mean elimination half-lives obtained by non-compartmental analysis and the beta half-life obtained by the compartmental method of estimation.

Using procedure NLIN of SAS, the plasma concentration versus time profile of BPD-MA_D is best described by a two-compartment model with intravenous administration in and elimination from the central compartment. All patients were successfully fitted to this pharmacokinetic model.

At all doses investigated, the maximal plasma concentration is generally observed at the end of the infusion and followed by a rapid decrease of the plasma concentration (alpha half-life ranging from 0.40 to 0.58 hours) (Appendix A.2). At approximately 2-3 hours, there is an inflexion of the plasma concentration curve. Thereafter, the disposition of BPD-MA_D has an apparent beta half-life of 4.57 to 5.72 hours. There is a good consistency between the mean elimination half-lives obtained by non-compartmental analysis and the Beta half-life obtained by the compartmental method of estimation.

8.3 Discussion of Efficacy and Pharmacokinetic Results

Interpretation of efficacy data in BPD 001 must be made with caution due to the limited number of patients and the large number of variables used. These variables included different drug dose, light dose, tumor size, tumor thickness, time of light application and length of follow-up for each tumor. Nonetheless, complete clinical tumor responses were obtained at both a low-drug-dose and high-light-dose combination or a high-drug-dose and low-light-dose combination.

The relationship between drug and light doses in achieving clinical response was presented by the logistic regression contour graphs. These graphs provide a basis for choosing efficacious drug-light dose combinations in future studies. From the logistic regression analyses presented by the contour graphs, for a probability of a complete response rate of $\geq 95\%$ in primary skin tumors, it is recommended to use a drug dose of ≥ 0.35 mg/kg and a light dose of ≥ 50 J/cm².

The pharmacokinetics of verteporfin, after a single intravenous infusion of a 45-minute duration, exhibits simple pharmacokinetics that are highly predictable. With an apparent elimination half-life of approximately 5-6 hours, verteporfin is rapidly cleared from the body and should not result in any accumulation with the intended dose regimens that call for single doses or doses separated by a minimum of 1 week. Also, verteporfin administration should not result in prolonged photosensitivity due to its rapid clearance.

9. SAFETY RESULTS

All patients enrolled in the study received verteporfin PDT. Safety was assessed in all patients over all courses from the start of verteporfin infusion to the end of the 3-month follow-up visits.

9.1 Extent of Exposure

Listing of Dosing Regimen: Appendix E.1.4

9.1.1 Exposure to Trial Treatment

For each patient a course of treatment included a single dose of verteporfin (between 0.15 mg/kg and 0.50 mg/kg) administered intravenously over a period of 45 minutes. A minimum of 1.5 and a maximum of 6 hours after the initiation of the verteporfin infusion (Time 0), the therapeutic light treatment (doses ranging from 25-150 J/cm²) was delivered to the lesion and surrounding normal tissue (10 cm²). Thirteen patients were infused with a single drug dose, but received two light doses on different treatment fields (Amendment 5). Extent of exposure to treatment is summarized in Table 13 below.

TABLE 13. Summary of Exposure to Drug and Light

Course	Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Patients ^a	Number of Lesions	Number of Treatment Fields
1	0.15	150	2	8	5
		75	1	3	3
		125	1	2	2
	0.25	150	8	29	20
		50	3	19	9
		100	5	16	12
		150	2	5	4
	0.30	25	3	9	8
		50	9	28	22
		75	5	10	9
	0.375	50	2	7	6
0.50		50	3	12	7
	Total	44	148	107	
2	0.15	150	1	8	3
		0.30	25	1	2
	0.30	50	2	15	6
		75	2	2	2
	Total	6	27	13	
3	0.30	50	1	6	3
		75	1	1	1
	Total	2	7	4	

^a Of the 35 patients enrolled in the study, 13 received 2 light doses on different treatment fields, 3 patients received two courses of PDT on separate days, and 1 patient received 3 courses of PDT. Since this column expressed exposure in terms of each drug and light combination, some of the patients were included several times opposite each light dose in each course.

9.1.2 Exposure to Concomitant Treatment

Listing of Concomitant Medications: Appendix E.4.7

Appendix E.4.7 provides a listing of all concomitant medications used throughout the study. The most common concomitant medication used was analgesics (for example, acetaminophen ± codeine or acetylsalicylic acid ± oxycodone). Approximately 75% of the patients received analgesics after receiving PDT treatment.

9.2 Overview of Adverse Events

Summary of All Adverse Events by Body System, Severity, and Relationship: Appendix A.4

Listing of Systemic Toxicity: Appendix E.4.1

Listing of Clinical Adverse Events: Appendix E.4.2

Table 14 summarizes the different important categories of adverse events.

TABLE 14. Safety Summary Table

	Treated Patients n=35	Patient Number
Patients with any adverse event	35	1-35
Patients with associated AE ^a	35	1-35
Deaths from any cause		
≤30 days post PDT	0	
>30 days post PDT	4	3, 11, 18, 29
Deaths due to AE	1 ^b	11 ^b
Withdrawal due to an adverse event	0	
Other serious AE	1	13

^a Associated adverse events are those considered to be definitely, probably or possibly related to the treatment. The severity could be mild, moderate or severe. (See Section 5.5.3.1 for definitions).

^b This adverse event was considered not related to treatment (Section 9.3.1) although it was assigned by the Investigator as possibly related to treatment.

Systemic toxicity data as reported using the NCI common toxicity is presented in Appendix E.4.1. However, since all systemic toxicity has also been collected as adverse events, the descriptive summary in the report will focus on adverse events (Summary Table Appendix A.4, Data Listing E.4.2).

9.2.1 All Adverse Events

Adverse events in the 35 patients who participated in the study are listed by body system, severity, and their association to therapy in Appendix E.4.2 and summarized in Table 15. Most of the adverse events occurred locally in the treatment fields during or post light exposure.

The most common systemic adverse event was nausea, which occurred in 23% (8/35) of patients. However, it was mild in all cases except one which was moderate. Other less

frequently occurring systemic adverse events which may or may not be related to treatment included pain, asthenia, headache, fever, vomiting, leukopenia, erythema, and dizziness. All these events occurred in 17% (6/35) patients and in most cases they were mild to moderate.

The most frequent adverse events which occurred locally in the treatment fields at the time of light exposure included warmth (49%), burning sensation (23%), and pain (20%). The most common adverse events which occurred within the treatment fields post PDT included pain (57%), edema (26%), pruritus (23%), erythema and tenderness (20% each). Most local treatment effects were the expected pharmacological action of PDT, and they were mostly mild to moderate in severity.

**TABLE 15. Summary of All Adverse Events
(Occurring in ≥5% of Patients)**

(Page 1 of 2)

BODY SYSTEM Adverse Event	Number (%)		Number of Events	Severity Grade of Events ^a		
	n=35			1	2	3
BODY AS A WHOLE	19	(54)	40			
Abdominal pain	2	(6)	2	0	2	0
Asthenia	6	(17)	7	2	4	1
Back pain	2	(6)	2	0	1	1
Face edema	3	(9)	3	0	2	1
Fever	6	(17)	6	5	1	0
Headache	6	(17)	7	3	3	1
Infection	2	(6)	2	2	0	0
Malaise	3	(9)	3	3	0	0
Neck pain	2	(6)	2	1	1	0
Pain	6	(17)	6	3	1	2
CARDIOVASCULAR	9	(26)	11			
Hypertension	3	(9)	3	2	0	1
Tachycardia	2	(6)	2	1	1	0
Vasodilatation	5	(14)	6	6	0	0
DIGESTIVE SYSTEM	10	(29)	19			
Anorexia	2	(6)	2	0	2	0
Diarrhea	2	(6)	2	1	1	0
Nausea	8	(23)	9	8	1	0
Vomiting	6	(17)	6	4	2	0
HEMIC AND LYMPHATIC	8	(23)	13			
Hypochromic anemia	2	(6)	3	3	0	0
Leukopenia	6	(17)	8 ^b	4	2	1
Reticulocytopenia	2	(6)	2	2	0	0
METABOLIC AND NUTRITIONAL	14	(40)	23			
Bilirubinemia	2	(6)	2	2	0	0
Hypercholesteremia	5	(14)	5	1	4	0
Hyperglycemia	3	(9)	3	1	1	1
Hyperlipemia	4	(11)	4	2	2	0
Peripheral edema	6	(17)	6	3	1	2
Weight loss	3	(9)	3 ^b	0	1	0
MUSCULOSKELETAL	2	(6)	2			
Myasthenia	2	(6)	2 ^b	1	0	0
NERVOUS SYSTEM	10	(29)	16			
Anxiety	2	(6)	2	1	1	0
Dizziness	6	(17)	7	6	1	0
Hypertonia	2	(6)	2	1	1	0
Paresthesia	2	(6)	3	3	0	0
Somnolence	2	(6)	2	2	0	0
ONCOLOGY	2	(6)	3			
Skin metastases	2	(6)	3	0	1	2
RESPIRATORY SYSTEM	7	(20)	14			
Cough	3	(9)	4	4	0	0
Dyspnea	3	(9)	6	2	0	4
Lung disorder	2	(6)	2	1	0	1
Rhinitis	2	(6)	2	1	1	0

^a Grade of Severity: 1 = mild, 2 = moderate, 3 = severe

^b Severity grade for some events were missing

**TABLE 15. Summary of All Adverse Events
(Occurring in ≥5% of Patients)**

(Page 2 of 2)

BODY SYSTEM Adverse Event	Number (%)		Severity Grade of Events ^a		
	of Patients n=35	Number of Events	1	2	3
SKIN AND APPENDAGES:					
NON-TREATMENT SITE					
Pruritus	4 (11)	4	3	0	1
Rash	6 (17)	7	7	0	0
Sweating	2 (6)	2	2	0	0
SKIN AND APPENDAGES:					
TREATMENT SITE DURING LASER					
Burning	8 (23)	9	8	1	0
Pain	7 (20)	14	2	7	5
Pruritus	6 (17)	6	6	0	0
Tingling	2 (6)	3	3	0	0
Warmth	17 (49)	30	20	8	2
SKIN AND APPENDAGES:					
TREATMENT SITES POST LASER					
Blanching	5 (14)	11	9	2	0
Blister	3 (9)	5	2	3	0
Discomfort	3 (9)	3	3	0	0
Edema	9 (26)	17	7	9	1
Erythema	7 (20)	19	8	11	0
Infection	2 (6)	3	3	0	0
Local eschar	4 (11)	18	2	10	6
Pain	20 (57)	42	20	19	3
Petechia	3 (9)	4	2	2	0
Pruritus	8 (23)	13	11	2	0
Purpura	6 (17)	10	2	6	2
Scab	2 (6)	4	2	2	0
Skin discoloration	3 (9)	5	4	1	0
Skin Necrosis	4 (11)	5	0	2	3
Stinging	3 (9)	3	2	1	0
Tenderness	7 (20)	10	6	4	0
Tight skin	2 (6)	2	1	1	0
Warmth	4 (11)	6	6	0	0
SPECIAL SENSES					
Amblyopia	2 (6)	3	3	0	0
Glare	3 (9)	3	3	0	0
Taste loss	2 (6)	2	2	0	0
Vision abnormalities	2 (6)	3	3	0	0
UROGENITAL					
Bacteriuria	2 (6)	2	2	0	0
Hematuria	3 (9)	3	2	1	0
Urine abnormalities	5 (14)	11	8	3	0

^a Grade of Severity: 1 = mild, 2 = moderate, 3 = severe

9.2.2 Associated Adverse Events

Summary table for all associated adverse events is presented in Table 16. Adverse event causal relationship definitions are presented in Section 5.5.3.1. The adverse event was considered to be associated with the study therapy, for the purpose of this report, if the causal relationship was reported as definite, probable, or possible. The most common associated

adverse events were facial edema, peripheral edema, and pain (9% each), and nausea, vomiting, and pruritus (6% each), most of them mild to moderate in severity. Pruritus or rash was reported as associated adverse events in 2 patients. From the timing and location of the events, they were mostly related to the PDT effect in an area adjacent to the treatment field or to photosensitivity erythema rather than to a hypersensitivity reaction.

**TABLE 16. Summary of All Associated^a Adverse Events
(All Patients)**

(Page 1 of 2)

BODY SYSTEM Adverse Event	No. (%) of Patients n=35		Number of Events	Severity Grade of Events ^b		
				1	2	3
BODY AS A WHOLE	8	(23)	10			
Chest pain	1	(3)	1	1	0	0
Facial edema	3	(9)	3	0	2	1
Fever	2	(6)	2	1	1	0
Malaise	1	(3)	1	1	0	0
Pain	3	(9)	3	1	0	2
CARDIOVASCULAR	2	(6)	2			
Hypertension	1	(3)	1	0	0	1
Vasodilation	1	(3)	1	1	0	0
DIGESTIVE SYSTEM	3	(9)	5			
Hepatitis	1	(3)	1	0	0	1
Nausea	2	(6)	2	1	1	0
Vomiting	2	(6)	2	1	1	0
HEMIC AND LYMPHATIC	2	(6)	3			
Hypochromic anemia	1	(3)	1	1	0	0
Leukocytosis	1	(3)	1	1	0	0
Purpura	1	(3)	1	0	1	0
METABOLIC AND NUTRITIONAL	4	(11)	4			
Edema	1	(3)	1	0	1	0
Peripheral edema	3	(9)	3	1	0	2
NERVOUS SYSTEM	1	(3)	1			
Anxiety	1	(3)	1	0	1	0
RESPIRATORY	1	(3)	1			
Asthma	1	(3)	1	1	0	0
SKIN AND APPENDAGES:						
GENERAL	3	(9)	3			
Pruritus	2	(6)	2	2	0	0
Sweat	1	(3)	1	1	0	0
TREATMENT SITE DURING LASER	26	(74)	67			
Burning	8	(23)	9	8	1	0
Discomfort	1	(3)	1	1	0	0
Erythema	1	(3)	1	0	1	0
Pain	7	(20)	13	2	6	5
Prickling	1	(3)	3	2	1	0
Pruritus	6	(17)	6	6	0	0
Stinging	1	(3)	1	1	0	0
Tingling	2	(6)	3	3	0	0
Warmth	17	(49)	30	20	8	2

^a Associated adverse events are those considered to be definitely, probably, or possibly related to treatment

^b Grade of Severity: 1 = mild, 2 = moderate, 3 = severe

**TABLE 16. Summary of All Associated^a Adverse Events
(All Patients)**

(Page 2 of 2)

BODY SYSTEM Adverse Event	No. (%) of Patients n=35		Number of Events	Severity Grade of Events ^b		
				1	2	3
SKIN AND APPENDAGES:						
TREATMENT SITE AFTER LASER	27	(77)	185			
Blanching	4	(11)	10	8	2	0
Blister	3	(9)	5	2	3	0
Burning	1	(3)	1	1	0	0
Discomfort	3	(9)	3	3	0	0
Dry skin	1	(3)	1	0	1	0
Ecchymosis	1	(3)	1	1	0	0
Edema	9	(26)	17	7	9	1
Erythema	7	(20)	19	8	11	0
Local eschar	4	(11)	18	2	10	6
Pain	20	(57)	42	20	19	3
Petechia	3	(9)	4	2	2	0
Pruritus	7	(20)	12	10	2	0
Purpura	6	(17)	10	2	6	2
Pustule	1	(3)	1	0	1	0
Scab	2	(6)	4	2	2	0
Serous discharge	1	(3)	1	1	0	0
Skin atrophy	1	(3)	2	2	0	0
Skin discoloration	3	(9)	5	4	1	0
Skin hypertrophy	1	(3)	2	2	0	0
Skin necrosis	4	(11)	5	0	2	3
Skin ulcer	1	(3)	1	0	1	0
Stinging	3	(9)	3	2	1	0
Tenderness	7	(20)	10	6	4	0
Tight skin	2	(6)	2	1	1	0
Warmth	4	(11)	6	6	0	0
SPECIAL SENSES						
Amblyopia	1	(3)	1	1	0	0
Conjunctivitis	1	(3)	1	1	0	0
Eye strain	1	(3)	1	1	0	0
Glare	2	(6)	2	2	0	0

^a Associated adverse events are those considered to be definitely, probably, or possibly related to treatment
^b Grade of Severity: 1 = mild, 2 = moderate, 3 = severe

9.3 Deaths, Withdrawals, and Other Serious Adverse Events

9.3.1 Deaths

Patient Capsule Summaries (Deaths): Appendix C.1
Listing of Medical History: Appendix E.1.2

Four patients died during the study period, three due to progressive metastatic malignant diseases and one as a result of progressive liver disease (Patients 3, 11, 18, and 29 respectively). Capsule summaries for these patients are presented in Appendix C.1.

Patient 11 was a 59-year-old man with basal cell carcinoma. He had elevated liver enzymes at baseline, a history of chronic liver disease, and was also a chronic carrier for the hepatitis B

virus. The patient received 0.50 mg/kg of verteporfin and 50 J/cm² light treatment of basal cell carcinomas. Hospitalization due to deterioration of liver functions, as indicated by elevations in bilirubin, alanine, and aspartate aminotransferase levels, occurred 71 days post treatment. The patient died of bleeding esophageal varices 81 days post treatment. The Investigator indicated that this patient's progressive liver disease was possibly related to treatment. Relationship of this serious adverse event is questionable however, based on the patient's history of liver disease, liver cirrhosis on autopsy indicating a chronic condition predating the study, and the fact that the patient was febrile and complaining of malaise immediately prior to PDT. The autopsy report indicated that the cause of gastrointestinal hemorrhage was dilated esophageal varices, which could only be produced by long-standing liver disease.

All other deaths were considered by the Investigator to be not related to treatment.

Patient 29 was a 69-year-old woman with breast cancer. She was hospitalized due to left pleural effusion, which was initially confined to the left hemithorax but spread to bilateral pleural involvement over a 1-month time frame. Prior to treatment for lesions due to metastatic breast cancer, the patient had radiologically documented evidence of left pleural effusion. This patient subsequently died 2 months later due to carcinoma with progressive metastases. The relationship to PDT was judged by the Investigator to be "remote".

Patients 3 and 18 died as a result of progressive metastatic diseases. *Patient 3* was found to have cerebral and CNS metastases. Increasing peripheral lymphadenopathy following treatment preceded the patient's death. The patient decline was not considered related to treatment in any way. *Patient 18* died due to respiratory arrest and progression of her underlying disease. An autopsy was not done.

9.3.2 Withdrawal Due to Adverse Events

No patients withdrew from the study due to adverse events.

9.3.3 Other Serious Adverse Events

Patient Capsule Summaries (Other Serious Adverse Events): Appendix C.3

There was one case of other serious adverse events (not causing death or withdrawal) reported.

Patient 13 was a 53-year-old man with Bowen's disease and cutaneous metastatic lesions. He received 0.375 mg/kg of verteporfin and 50 J/cm² light for treatment of 3 metastatic carcinoma lesions on the right leg. This patient had had a previous incidence of trauma to the same leg that was treated with PDT. Edema of the leg developed 2 or 3 days after treatment, became

severe and lasted approximately 3 weeks. This severe edema of the treated leg accounted for a 17-lb weight gain, developing throughout the first week posttreatment. The edema completely resolved with elevation of the leg, tensor bandages, and bed rest. This event was judged to be possibly related to study treatment. A capsule summary of this patient is presented in Appendix C.3.

9.4 Laboratory Data

Summary of Clinical Laboratory Data: Appendix A.3
SAS Output on Laboratory Data Analysis: Appendix B.2
Listing of Laboratory Results: Appendix E.4.3

Samples were drawn for laboratory tests at screening and on Days 1, 2, 3, and 7 posttreatment. Individual Laboratory Measurements are listed by patient in Appendix E.4.3.

Significant change from baseline was evaluated using a McNemar's test for matched pairs. Table 17 below displays all the laboratory parameters in the study that showed a significant difference from the baseline value at any study day. Summary tables showing individual patient changes from baseline for each laboratory parameter are in Appendix A.3.

TABLE 17. Laboratory Values with Significant Changes from Baseline

Evaluation	Day 1	Day 2	Day 3	Day 7
Protein	*			
Albumin	*	*	*	
Super oxidase dismutase	*			
Phosphate	*			
Calcium			*	
Neutrophils		*		
Monocytes			*	
Hematocrit				*

* Parameters that showed a significant difference ($p \leq 0.05$) from baseline were denoted by an asterisk

Most changes were considered not clinically significant as they did not have a consistent pattern or the parameter was in the abnormal range even before dosing. Although some of the parameters were statistically significantly different from baseline, they were still within the normal range for the most part. In the Protocol, an adverse event was considered possibly associated to treatment if the event followed a reasonable temporal sequence from drug administration to treatment; or the event could not have been produced by the patient's clinical state or by other modes of therapy administered to the patient.

Only three laboratory changes were considered clinically significant and possibly associated to treatment.

Patient 16, a 40-year-old female with metastatic skin tumors, had an increase in RBC count post PDT ($4.11 \times 10^{12}/L$ and $4.24 \times 10^{12}/L$ respectively at 24 and 48 hours post drug infusion versus $3.93 \times 10^{12}/L$ at baseline). The RBC count returned to $3.83 \times 10^{12}/L$ at 72 hours.

Patient 26, a 71-year-old female with metastatic skin tumors, had turbid urine 24 hours after verteporfin infusion. Her urine sample continued to be cloudy in appearance on Day 7.

Patient 27, a 77-year-old male with multiple BCC, had a lower than normal hemoglobin level (122 g/L) at baseline. Twenty-four hours post treatment, his hemoglobin level was at 113 g/L. The hemoglobin level remained low on all sampling dates. On Day 7, the last date of sampling, the level was at 113 g/L.

9.5 Vital Signs and Other Physical Findings

Listing of Vital Signs: Appendix E.4.4
Listing of Eye Examination Results: Appendix E.4.5
Listing of Electrocardiogram Results: Appendix E.4.6

No treatment related clinically significant abnormality in vital signs or other physical findings (e.g. ECG and ophthalmic examination) was recorded. Individual listings of vital signs, eye examination, and ECG results are presented respectively in Appendices E.4.4, E.4.5, and E.4.6.

9.6 Special Safety Variables

9.6.1 Duration of Skin Photosensitivity Results

Listing of Skin Photosensitivity of Normal Skin: Appendix E.4.8

Photosensitivity testing was accomplished using an Oriel broad light spectrum solar simulator. Various light doses up to $215 J/cm^2$ were delivered. Since all 30 patients tested had a baseline MED in excess of the highest dose tested ($215 J/cm^2$), this dose was assumed as the baseline MED for all patients. The duration of skin photosensitivity was presented as the number of days post verteporfin infusion before the MED returned to $215 J/cm^2$ (Table 18).

TABLE 18. Time for the Minimal Erythematous Dose to be at 215 J/cm² following a Single Intravenous Injection of Verteporfin

Drug Dose (mg/kg)	Number of Patients	Mean Time (Days)	Minimum Time (Days)	Maximum Time (Days)
0.15	3	2.0	2	2
0.20	8	2.6	2	4
0.25	8	2.9	2	3
0.30	6	4.8	4	7
0.375	2	5.5	5	6
0.50	3	6.7	6	8

For drug doses between 0.15 mg/kg and 0.50 mg/kg, mean duration of normal skin photosensitivity to 215 J/cm² of broad spectrum light was 2 and 6.7 days respectively post verteporfin administration. The duration of photosensitivity was directly related to the dose of verteporfin given. Listings of skin photosensitivity results is presented in Appendix E.4.8. Figure 5 displays photosensitivity expressed as the reciprocal of the MED.

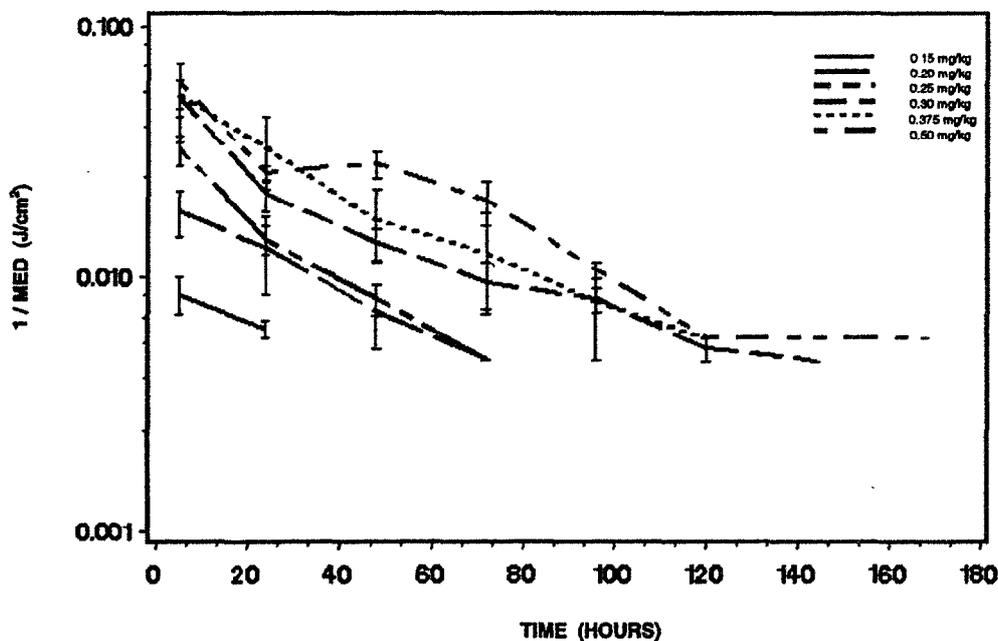


FIGURE 5. Mean Cutaneous Photosensitivity to UVA/Visible Light Following Verteporfin Administration

9.6.2 PDT-induced Skin Reaction in Peritumoral Area

Listing of Local Non-tumor Skin Toxicity: Appendix E.4.9

Each treatment field was to have, at some point, a 1 cm torus of peritumoral area (normal skin within the treatment field). Peritumoral PDT-induced skin reactions were evaluated in this normal skin according to skin reaction criteria on a scale of Grade 1 to Grade 4 (Appendix D.6.2).

Table 19 summarizes the peritumoral PDT-induced skin reactions for all treatment fields. The 182 tumors treated by PDT were located in 124 treatment fields. Of the 124 treatment fields, 8 fields (6%) showed necrosis of apparently normal skin (Grade 4). Forty-four percent of treatment fields developed Grade-3 skin reactions, 40% developed Grade-2 skin reactions, and 9% developed Grade-1 skin reactions. The skin of all patients including those with Grade-4 reactions healed well without incident and with good cosmetic results. Individual listings of PDT-induced peritumoral skin reaction is presented in Appendix E.4.9.

TABLE 19. Peritumoral PDT Skin Reactions for all Treatment Fields

Verteporfin Dose (mg/kg)	Light Dose (J/cm ²)	Number of Treatment Fields	Number (%) of Treatment Fields							
			Grade 1 ^a		Grade 2 ^a		Grade 3 ^a		Grade 4 ^a	
0.15	150	8	1	(13)	7	(88)	0	(0)	0	(0)
0.20	75	3	0	(0)	1	(33)	2	(67)	0	(0)
	125	2	0	(0)	0	(0)	2	(100)	0	(0)
	150	20	1	(5)	10	(50)	6	(30)	3	(15)
0.25	50	9	6	(67)	3	(33)	0	(0)	0	(0)
	100	12	0	(0)	10	(83)	1	(8)	1	(8)
	150	4	0	(0)	1	(25)	3	(75)	0	(0)
0.30	25	10	2	(20)	2	(20)	6	(60)	0	(0)
	50	31	1	(3)	6	(19)	24	(77)	0	(0)
	75	12	0	(0)	3	(25)	9	(75)	0	(0)
0.375	50	6	0	(0)	2	(33)	2	(33)	2	(33)
0.50	50	7	0	(0)	5	(71)	0	(0)	2	(29)
	Total	124	11	(9)	50	(40)	55	(44)	8	(6)

^a Definitions:

- Grade 1 - scattered macular or papular eruption or erythema that is asymptomatic and minimally perceptible.
- Grade 2 - scattered macular or papular eruption or erythema with pruritus or other associated symptoms or palpable edema.
- Grade 3 - vesicle eruption or severe erythema or palpable edema extending beyond the area of exposure.
- Grade 4 - skin ulceration other than superficial ulceration resulting from evolution of a vesicle.

In the Protocol, dose adjustment was determined by assessing both systemic toxicity and peritumoral PDT-induced skin reaction. No treatment related systemic toxicity had resulted in dose adjustment. However, further dose escalation was halted when Grade-4 PDT-induced

skin reactions were observed in 2 of the 3 patients (Patients 10 and 11) receiving PDT at a drug dose of 0.5 mg/kg and 50 J/cm² of light. The lowering of drug dose to 0.375 mg/kg in Patients 12 and 13 did not abolish Grade-4 skin reaction completely. The reaction occurred in 2 of the 6 peritumoral areas.

Amendment 4 reduced the drug dose to 0.25 mg/kg for the subsequent 2 patients, but increased the light dose to 150 J/cm². The amendment also allowed different treatment fields to receive different light doses. The Protocol's definition of local MTD as doses resulting in less than Grade 3 and 4 skin reactions proved to be very conservative since Grade 3 or higher skin reactions were noted in almost all drug and light dose combinations except at 0.15 mg/kg + 150 J/cm² and 0.25 mg/kg + 50 J/cm². However, applying the Protocol's criteria, the MTD would be either 0.15 mg/kg + 150 J/cm² or 0.25 mg/kg + 50 J/cm².

9.7 Discussion of Safety Results

In this first study of verteporfin in humans, systemic safety of verteporfin and the PDT-induced reactions occurring at the peritumoral area were carefully assessed. The data indicated that verteporfin had a safe systemic profile. Treatment-related systemic adverse events were uncommon, and most occurrences were below 9%. No systemic adverse events considered to be related to treatment were considered clinically significant.

In terms of local skin reactions within the treatment field, Grade-3 and -4 skin reactions were observed in most drug- and light-dose combinations studied. This made the Protocol's definition of MTD unrealistic. The high-grade skin reactions could also be due to the presence of residual tumors in the peritumoral area which were not visible to the naked eye at the time of examination, or due to the difference in skin types between patients and the fact that some patients have more sensitive skin. The results suggest also that the differential in verteporfin accumulation between tumor and normal skin may be insufficient to allow for a reproducible highly selective PDT response. This agrees with the preclinical data from mice that showed only a tumor to normal skin ratio of approximately 2:1 (7).

Tumor eradication by PDT can occur as a result of either direct cell kill or ischemic necrosis by neovasculature shutdown, or both of these mechanisms (6). The end result was necrosis of the PDT-treated tumors. If the peritumoral area contained microscopic cancerous cells or the selectivity between tumors and normal skin was not high, it would not be unexpected to see a Grade 3 or higher reaction in the peritumoral area. These reactions would even be necessary to ensure the efficacy of the treatment in achieving complete tumor eradication. The reactions could be limited by decreasing the torus of normal skin surrounding a lesion that will be exposed to light. For example, the light exposure area could be limited to a circumferential margin of 3-4 mm which is the same tumor margin currently used in excision by most

surgeons. With the 3-4 mm margin, it will not be critical to ensure that peritumoral skin within the PDT-treated area has to be below a certain skin reaction score, since no normal skin (apart from the peritumoral margin) will be exposed to light. This peritumoral tissue would have been removed anyway with standard therapy to ensure an adequate tumor-free margin. Regardless of the PDT skin reactions in the tumors and peritumoral area, good cosmetic results were reported by Investigators for the whole treatment field even after a Grade-4 skin reaction.

The time for patients to have an MED value of 215 J/cm^2 was approximately 2 days after receiving a verteporfin dose of 0.15 mg/kg . The duration increased to 6.7 days at 0.50 mg/kg of verteporfin. The light dose used in the assessment was relatively high (215 J/cm^2 was equivalent to 0.5 to 1 hour of midday exposure in the summer in New Mexico). Most cities do not have sun intensity as intense as New Mexico. Also, in practice, patients do not normally need to wait until the skin photosensitivity level has returned to undetectable level before resuming outdoor activities. Hence, the actual time required for a patient infused with 0.50 mg/kg of verteporfin to avoid long bright sunlight exposure should be less than 6.7 days.

10. DISCUSSION AND OVERALL CONCLUSIONS

The mean duration of normal skin photosensitivity to broad spectrum light following verteporfin infusion was found to be dose dependent, ranging from 2 days at 0.15 mg/kg of verteporfin to 6.7 days at 0.5 mg/kg. However, the broad spectrum light dose (215 J/cm²) used was extremely high and in most cities the sun intensity will not be at that level. Therefore, the time required for patients to avoid long bright sunlight exposure after verteporfin infusion will be less than those expressed in this report.

In the Protocol, MTD was defined as the highest safely tolerated drug- and light-dose combination. A drug- and light-dose combination was considered to be safe if treatment related systemic toxicity was below Grade 2 according to the NCI Common Toxicity Criteria and/or PDT-induced skin reaction in the peritumoral area was below Grade 3. None of the patients in this study experienced a Grade-2 treatment-related systemic toxicity.

Two drug- and light-dose combinations (0.15 mg/kg of drug + 150 J/cm² of light and 0.25 mg/kg + 50 J/cm² light) showed no Grade-3 skin reaction in the peritumoral area; hence, two MTDs for the study. This was not surprising, because PDT is due to a combined effect of both drug and light. Generally, the two parameters are reciprocal of each other (i.e., to have the same PDT effect, a low drug dose will require a higher light dose; whereas a high drug dose will need a lower light dose). Therefore, an MTD could be reached for every drug dose by escalating the light dose sequentially. Only a study that has one of the parameters fixed (either drug or light) can produce a unique MTD.

However, severity of skin reaction in the peritumoral area should not be used as a determining factor for selecting drug and light doses in future studies, since this level of reaction may be needed to eradicate microscopic tumor in the peritumoral area and since all treatment fields (regardless of severity in skin reaction) healed well with good cosmetic outcome. Furthermore, skin reaction could be limited by reducing the circumferential peritumoral area to 3-4 mm, which is the standard margin used in surgical excision of cutaneous tumors.

High complete tumor and patient response rate was observed in several drug- and light-dose combinations. The contour graphs generated from logistic regression analyses provide a basis for choosing an efficacious drug and light combinations for future development of PDT with verteporfin for cutaneous lesions. Regimens with a drug dose of ≥ 0.35 mg/kg and a light dose of ≥ 50 J/cm² would be associated with the probability of a CR rate of $\geq 95\%$ in primary skin tumors.

The disposition of verteporfin in the dose range studied shows good dose-related proportionality of drug exposure and little dose-related variation in clearance and distribution parameters. With an apparent elimination half-life of approximately 5-6 hours, verteporfin is rapidly cleared from the body and should not result in any accumulation with the intended dose regimens that call for single doses or repeated doses separated by a minimum of 1 week.

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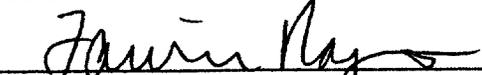
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CLINICAL STUDY REPORT: BPD 001 AMENDMENT NO. 1 DATED 28 JULY 1999
DRUG NAME: VERTEPORFIN FOR INJECTION
TITLE AND NAME: PHOTODYNAMIC THERAPY WITH BENZOPORPHYRIN
DERIVATIVE MONOACID A RING (BPD-MA) IN THE
TREATMENT OF MALIGNANT CUTANEOUS LESIONS DATED
22 JANUARY 1999

PREPARED BY:



Laurie Haynes
Senior Manager, Medical Information

28 July 99
Date



Xiang Yao Su, PhD
Statistician

July 29, 1999
Date

The undersigned attest to the following:

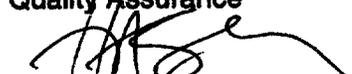
1. Reviewed the amendment
2. Agreed to its contents

APPROVED BY:



Michele Gervais, BSc
Quality Assurance

Jul 28/99
Date



Andrew Strong, PhD
Director, Clinical Research

28 July 99.
Date



Jean-Marie Houle, PhD
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28 July 99
Date



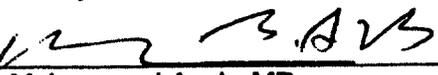
Agnes Chagn, PhD
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Date



Noel Buskard, MD, FRCP, FACP
Safety and Medical Officer

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Date



Mohammad Azab, MD
Vice President, Clinical Research

28 July 99
Date

CLINICAL STUDY REPORT: BPD 001 AMENDMENT NO. 1 DATED 28 JULY 1999
DRUG NAME: VERTEPORFIN FOR INJECTION
TITLE AND NAME: PHOTODYNAMIC THERAPY WITH BENZOPORPHYRIN
DERIVATIVE MONOACID A RING (BPD-MA) IN THE
TREATMENT OF MALIGNANT CUTANEOUS LESIONS DATED
22 JANUARY 1999

REVISION NO.: 1

Reason for Revision: To correct the time of light application stated in the Synopsis.

Amendment: Page vi, Synopsis, Study Description (Methods and Investigational Plan), Treatment (Identity of Investigational Product), 4th line is changed:

From:

6 hours post the end of verteporfin infusion.

To:

6 hours after the start of verteporfin infusion.

REVISION NO.: 2

Reason for Revision: To correct the list of laboratory tests in footnote "b" of Table 1, which is incomplete.

Amendment: Page 14, Table 1, footnote "b" of Section 5.4.1, Pretreatment Procedures (-1 Month to -2 Days) is replaced by the following:

Laboratory tests included: hematology (red blood cell count, reticulocytes, hemoglobin, hematocrit, white blood cell count, neutrophils, lymphocytes, eosinophils, monocytes, basophils, bands, and platelets), serum chemistry (sodium, potassium, chloride, CO₂, glucose, BUN, creatinine, total protein, albumin, calcium, phosphorus, total bilirubin, direct bilirubin, AST (SGOT), ALT (SGPT), LDH, alkaline phosphatase, uric acid, cholesterol, and triglycerides), and urinalysis (appearance, specific gravity, pH, glucose, blood, protein, urobilinogen, ketones, and microscopic findings).

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REVISION NO.: 3

Reason for Revision: To include information on the patient who provided samples for pharmacokinetic analysis twice, under two different patient numbers and two different doses.

Amendment: Page 35, Section 8.2, Pharmacokinetic Results, is replaced. The following statement is changed:

Pharmacokinetic data are available for 21 patients who received single intravenous drug doses of 0.15, 0.20, 0.25, 0.375 or 0.50 mg/kg.

And the following statement is added:

Of the 21 patients who provided plasma samples for pharmacokinetic analysis, one patient provided two sets of samples after receiving two different doses (0.50 and 0.15 mg/kg) more than a year apart. Her patient number was 9 for the first dose (0.50 mg/kg) and 25 for the second dose (0.15 mg/kg). Therefore, 22 sets of plasma samples are included in the analyses.

Page vii, Synopsis, is replaced. The following statement, under Pharmacokinetic Results, is changed:

From:

Pharmacokinetic data was available from 22 patients who received a single intravenous dose of 0.15, 0.20, 0.25, 0.375, and 0.50 mg/kg of verteporfin.

To:

Pharmacokinetic data was available from 22 sets of plasma samples, from 21 patients who received a single intravenous dose of 0.15, 0.20, 0.25, 0.375, or 0.50 mg/kg of verteporfin.

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REVISION NO.: 4

Reason for Revision: To correct errors in Appendix A.4, Summary of All Adverse Events by Body System, Severity and Relationship.

Amendment: Appendix A.4 is replaced, with the following corrections:

- Inclusion of 4 events of "Death" under "Body As A Whole"
- Change of the number of events of "Discomfort" under "Skin and Appendages: Treatment Site After Laser" from 4 to 3, with all 3 mild in severity
- Inclusion of the event of "Skin Ulcer" under "Skin and Appendages: Treatment Site After Laser"

REVISION NO.: 5

Reason for Revision: To add an adverse event term for Patient 16, to supplement Appendix E.4.2. The adverse event term was omitted from this appendix.

Amendment: A page entitled "ADVERSE EVENT Patient 16 (BURNING)," which contains information from the BPD 001 database, is added as a supplement to Appendix E.4.2.

REVISION NO.: 6

Reason for Revision: To add analytical methods description to the report.

Amendment: Appendix F, Analytical Report, is added.

Page v, Table of Contents, is replaced.

Page 58, Section 12, Study Appendices, is replaced.

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REVISION NO.: 7

Reason for Revision: To correct the equation regarding compartmental pharmacokinetic analysis.

Amendment: Page 24, Section 5.8.2.3, Analysis of Pharmacokinetics, is replaced. The following is changed:

From: $C_p = A e^{-\alpha t} + B e^{-\beta t}$
To: $C_p = A e^{(-\alpha \cdot t)} + B e^{(-\beta \cdot t)}$

REVISION NO.: 8

Reason for Revision: To correct the pharmacokinetics data to correspond to the verified analytical report.

Amendment: Page vii, Synopsis, Pharmacokinetic Results, is replaced. The following is changed:

From:
At all doses investigated, the maximal plasma concentration is observed at the end of the infusion (ranged from 0.55 – 1.88 µg/mL for doses between 0.15 mg and 0.50 mg/kg) and was followed by rapid decline (alpha half-life ranging from 0.26 to 0.74 hours and beta half-life of 3.88 to 6.52 hours).

To:
At all doses investigated, the maximal plasma concentration is observed at the end of the infusion (ranged from 0.68 – 1.87 µg/mL for doses between 0.15 mg and 0.50 mg/kg) and was followed by rapid decline (alpha half-life ranging from 0.25 to 0.59 hours and beta half-life of 4.7 to 6.3 hours).

Page viii, Synopsis, Study Conclusions #4, is replaced. The following is changed:

From:
With an apparent elimination half-life of 5-7 hours, . . .

To:
With an apparent elimination half-life of 5-6 hours, . . .

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REVISION NO.: 8 (continued)

Page 35, Section 8.2, Pharmacokinetic Results, is replaced. The following is added:

Data past the 24.75 hour sampling time was below the quantifiable level in all patients except for one single value. Consequently, this data is not included in the pharmacokinetic calculations or in the Appendix E.3.

Pages 36-40, Section 8.2, Pharmacokinetic Results, are replaced. Both figures on page 36 are replaced. Numbers in Table 12 and corresponding text (page 37) are updated. Text is updated on pages 37-40.

Page 55, Section 10, Discussion and Overall Conclusions, is replaced. The last paragraph was changed:

From:

With an apparent elimination half-life of approximately 5-7 hours, . . .

To:

With an apparent elimination half-life of approximately 5-6 hours, . . .

The following appendices are replaced:

A.1.1
A.1.2
A.1.3
A.1.4

A.2.1
A.2.2
A.2.3
A.2.4

B.3

E.3.1

APPENDIX A — SUMMARY TABLES AND GRAPHS

A.1. Summary of Pharmacokinetic Results for Regioisomer BPD-MA_C (CL 315,555)

- A.1.1 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_C Following a 45-Minute IV Infusion of Verteporfin (linear scale)
- A.1.2 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_C Following a 45-Minute IV Infusion of Verteporfin (semi-log scale)
- A.1.3 Mean Pharmacokinetic Data for BPD-MA_C - Noncompartmental Analysis
- A.1.4 Mean Pharmacokinetic Data for BPD-MA_C - Compartmental Analysis

A.2 Summary of Pharmacokinetic Results for Regioisomer BPD-MA_D (CL 315,585)

- A.2.1 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion of Verteporfin (linear scale)
- A.2.2 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion of Verteporfin (semi-log scale)
- A.2.3 Mean Pharmacokinetic Data for BPD-MA_D - Noncompartmental Analysis
- A.2.4 Mean Pharmacokinetic Data for BPD-MA_D - Compartmental Analysis

A.3 Summary of Clinical Laboratory Data

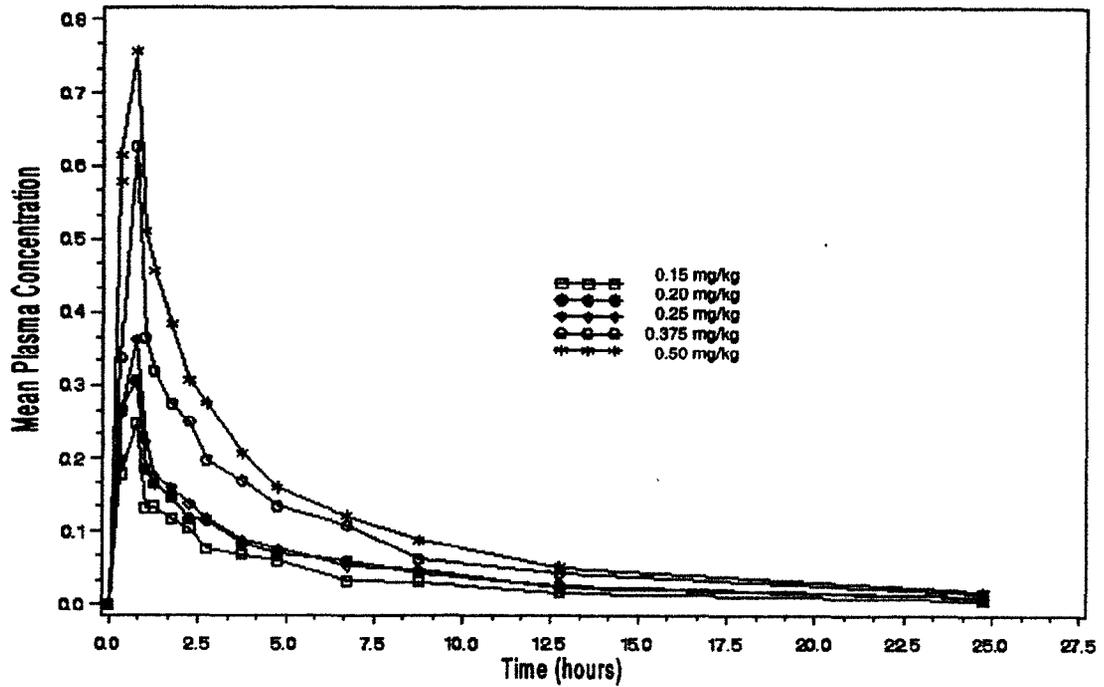
- A.3.1 Summary of Change from Baseline in Hematology Parameters
- A.3.2 Summary of Change from Baseline in Blood Chemistry Parameters
- A.3.3 Change from Baseline in Urinalysis Parameters

A.4 Summary of All Adverse Events by Body System, Severity, and Relationship

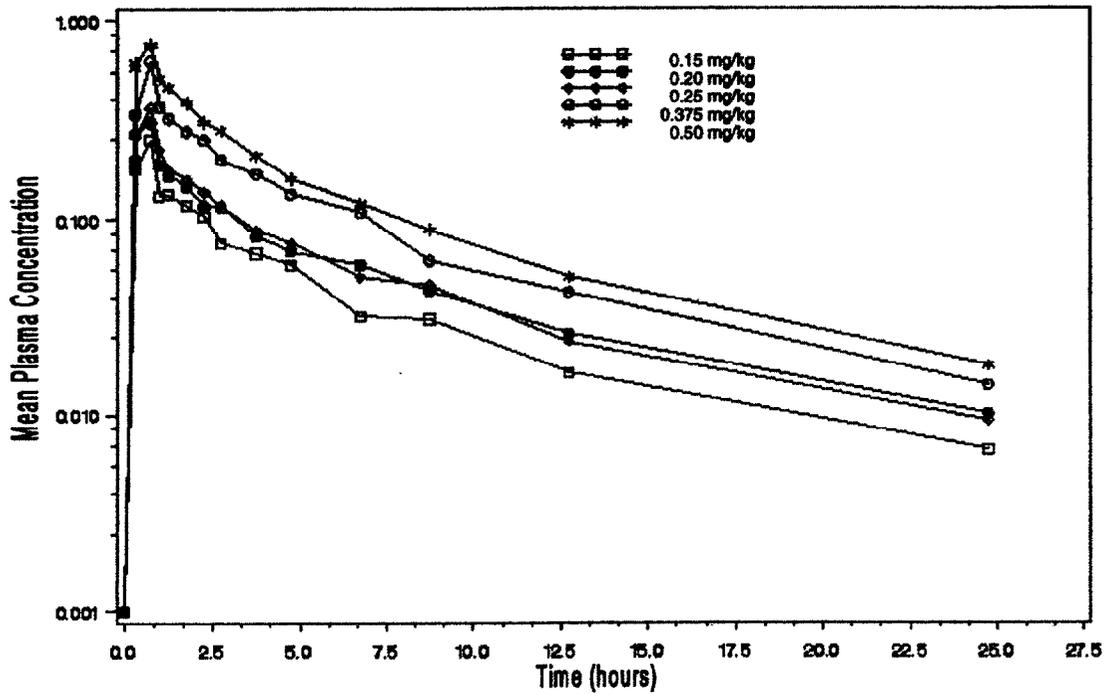
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- A.1.3 Mean Pharmacokinetic Data for BPD-MA_C - Noncompartmental Analysis
- A.1.4 Mean Pharmacokinetic Data for BPD-MA_C - Compartmental Analysis

APPENDIX A.1.1
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_c Following a 45-Minute IV Infusion Of Verteporfin
(Linear Scale)



APPENDIX A.1.2
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA_c Following a 45-Minute IV Infusion Of Verteporfin
(Semi-Log Scale)



APPENDIX A.1.3
Mean Pharmacokinetic Data for BPD-MA_C - Noncompartmental Analysis

No. of Patients	Drug Dose (mg/kg)	C _{max}		AUC ₀₋₂₄		AUC _{0-∞}		T _{1/2}		V _{ss}		CL	
		(µg/mL)	SD	(µg.hr/mL)	SD	(µg.hr/mL)	SD	(hr)	SD	(L/kg)	SD	(mL/hr/kg)	SD
3	0.15	0.26	0.08	0.92	0.35	1.00	0.33	6.71	1.08	0.56	0.14	82.94	34.26
7	0.20	0.31	0.05	1.24	0.27	1.35	0.32	7.34	1.14	0.64	0.18	78.15	22.01
8	0.25	0.38	0.04	1.23	0.28	1.32	0.31	5.95	1.75	0.64	0.06	99.69	25.80
2	0.38	0.63	0.02	2.16	0.20	2.29	0.27	6.24	1.05	0.57	0.04	82.36	9.81
3	0.50	0.76	0.20	2.83	0.88	3.00	1.01	6.28	0.97	0.57	0.14	90.28	32.17

APPENDIX A.1.4
Mean Pharmacokinetic Data for BPD-MA_c - Compartmental Analysis

No. of Patients	Drug Dose (mg/kg)	BPD-MA _c							
		α	SD	T _{1/2α} (hr)	SD	β	SD	T _{1/2β} (hr)	SD
2	0.15	2.76	0.62	0.26	0.06	0.12	0.03	6.17	1.41
6	0.20	1.88	0.81	0.48	0.36	0.11	0.01	6.52	0.97
8	0.25	1.60	0.80	0.53	0.23	0.13	0.04	5.79	1.49
2	0.38	1.64	0.19	0.43	0.05	0.12	0.02	5.67	0.84
3	0.50	1.03	0.42	0.74	0.27	0.11	0.01	6.16	0.59

A.2 Summary of Pharmacokinetic Results for Regioisomer BPD-MA_D (CL 315,585)

- A.2.1 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion of Verteporfin (linear scale)
- A.2.2 Plasma Concentration Versus Time Profiles of Regioisomer BPD-MA_D Following a 45-Minute IV Infusion of Verteporfin (semi-log scale)
- A.2.3 Mean Pharmacokinetic Data for BPD-MA_D - Noncompartmental Analysis
- A.2.4 Mean Pharmacokinetic Data for BPD-MA_D - Compartmental Analysis

APPENDIX A.2.1
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA₀ Following a 45-Minute IV Infusion Of Verteporfin
(Linear Scale)

