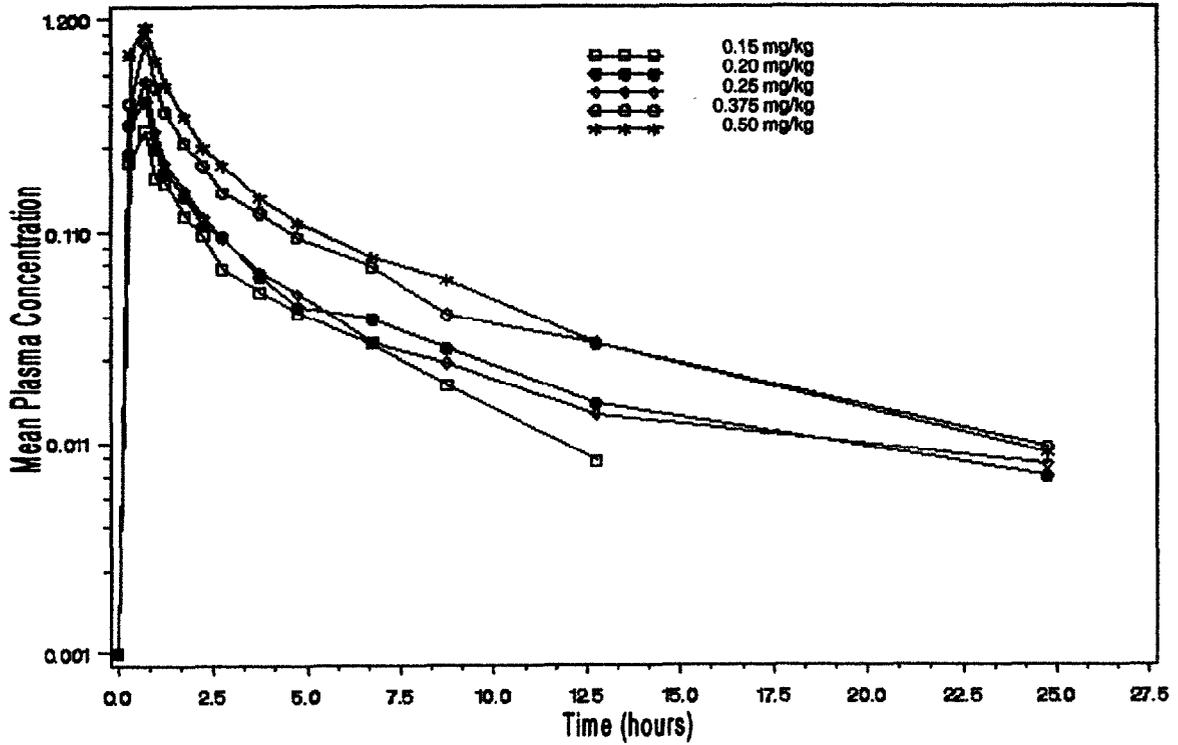


APPENDIX A.2.2
Plasma Concentration Versus Time Profiles
of Regioisomer BPD-MA₀ Following a 45-Minute IV Infusion Of Verteporfin
(Semi-Log Scale)



APPENDIX A.2.3
Mean Pharmacokinetic Data for BPD-MA₀ - Non Compartmental 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	0.41	0.15	1.07	0.63	1.15	0.69	3.84	0.14	0.28	0.18	84.64	51.56
6	0.20	0.48	0.09	1.10	0.35	1.18	0.35	5.06	1.52	0.42	0.13	92.30	32.51
8	0.25	0.60	0.05	1.13	0.30	1.20	0.31	4.73	1.45	0.43	0.05	109.91	27.87
2	0.38	0.94	0.06	2.10	0.19	2.19	0.22	6.26	0.40	0.48	0.01	85.96	8.51
3	0.50	1.11	0.29	2.70	0.42	2.78	0.43	5.68	0.33	0.43	0.10	91.39	13.09

APPENDIX A.2.4
Mean Pharmacokinetic Data for BPD-MA_D - Compartmental Analysis

No. of Patients	Drug dose (mg/kg)	BPD-MA _D							
		α	SD	$T_{1/2\alpha}$ (hr)	SD	β	SD	$T_{1/2\beta}$ (hr)	SD
3	0.15	1.54	0.58	0.49	0.18	0.18	0.04	3.88	0.73
6	0.2	1.86	0.32	0.38	0.07	0.16	0.04	4.53	1.08
8	0.25	1.54	0.58	0.51	0.19	0.15	0.06	5.55	3.15
2	0.375	1.33	0.12	0.53	0.05	0.11	0.01	6.19	0.51
3	0.5	1.14	0.15	0.62	0.09	0.13	0.01	5.44	0.34

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

APPENDIX A.3.1
Summary of Change from Baseline in Hematology Parameters

BASELINE/OBSERVATION

PARAMETER	VISIT	NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
BAND NEUTROPHILS	DAY 1	20	0	0	11
	DAY 2	19	1	0	11
	DAY 3	20	0	0	11
	DAY 7	18	0	0	10
	OPTIONAL	3	0	0	3
BASOPHILS	DAY 1	36	1	1	1
	DAY 2	36	0	1	1
	DAY 3	34	4	2	0
	DAY 7	32	2	0	2
	OPTIONAL	7	0	0	0
EOSINOPHILS	DAY 1	36	0	2	1
	DAY 2	36	0	2	1
	DAY 3	37	0	2	1
	DAY 7	34	0	1	1
	OPTIONAL	6	0	1	0
HEMATOCRIT	DAY 1	16	6	4	7
	DAY 2	13	9	3	8
	DAY 3	16	6	1	10
	DAY 7	10	10	1	10
	OPTIONAL	3	1	0	7
HEMOGLOBIN	DAY 1	14	2	2	20
	DAY 2	15	1	2	20
	DAY 3	17	0	2	20
	DAY 7	12	3	2	20
	OPTIONAL	2	1	1	6
LYMPHOCYTES	DAY 1	27	4	4	4
	DAY 2	25	6	2	6
	DAY 3	32	0	1	7
	DAY 7	21	6	3	5
	OPTIONAL	1	3	2	1
MONOCYTES	DAY 1	31	6	2	0
	DAY 2	31	6	2	0
	DAY 3	33	5	0	2
	DAY 7	29	5	1	1
	OPTIONAL	3	3	1	0
NEUTROPHILS	DAY 1	26	7	3	3
	DAY 2	25	7	1	5
	DAY 3	29	4	1	5
	DAY 7	25	5	3	2
	OPTIONAL	2	2	2	1

(CONTINUED)

APPENDIX A.3.1
Summary of Change from Baseline in Hematology Parameters

PARAMETER	VISIT	BASELINE/OBSERVATION			
		NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
PLATELETS	DAY 1	38	0	0	0
	DAY 2	38	0	0	0
	DAY 3	39	0	0	0
	DAY 7	36	0	0	0
	OPTIONAL	9	1	0	0
RBC	DAY 1	19	5	6	8
	DAY 2	19	5	4	10
	DAY 3	21	4	3	11
	DAY 7	18	5	6	8
	OPTIONAL	2	1	2	4
RETICULOCYTE CO	DAY 1	26	0	1	3
	DAY 2	25	2	4	0
	DAY 3	23	3	4	0
	DAY 7	26	1	3	0
	OPTIONAL	3	0	0	1
WBC	DAY 1	28	5	2	4
	DAY 2	31	2	1	4
	DAY 3	34	0	3	3
	DAY 7	30	2	2	4
	OPTIONAL	7	2	0	2

APPENDIX A.3.2
Summary of Change from Baseline in Blood Chemistry Parameters

BASELINE/OBSERVATION

PARAMETER	VISIT	NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
ALT (SGPT)	DAY 1	27	1	2	3
	DAY 2	26	2	2	3
	DAY 3	28	0	1	3
	DAY 7	22	2	2	3
	OPTIONAL	2	2	0	1
AST (SGOT)	DAY 1	36	1	2	1
	DAY 2	35	1	2	1
	DAY 3	36	1	1	2
	DAY 7	31	3	2	1
	OPTIONAL	5	0	0	1
Albumin	DAY 1	10	5	0	16
	DAY 2	9	6	0	16
	DAY 3	9	6	0	16
	DAY 7	12	2	0	14
	OPTIONAL	2	3	0	1
Alkaline Phosph	DAY 1	33	1	2	3
	DAY 2	33	0	2	3
	DAY 3	34	1	2	3
	DAY 7	32	0	2	3
	OPTIONAL	3	1	2	0
BUN	DAY 1	17	1	1	20
	DAY 2	15	2	1	21
	DAY 3	17	1	2	20
	DAY 7	15	2	3	16
	OPTIONAL	3	0	0	1
Calcium	DAY 1	15	4	0	18
	DAY 2	16	2	0	19
	DAY 3	13	6	0	19
	DAY 7	17	0	0	18
	OPTIONAL	1	0	0	1
Carbon Dioxide	DAY 1	30	2	6	1
	DAY 2	31	1	6	1
	DAY 3	31	2	7	0
	DAY 7	24	5	4	3
	OPTIONAL	2	1	0	1
Chloride	DAY 1	30	5	3	1
	DAY 2	30	6	1	2
	DAY 3	33	3	3	1
	DAY 7	31	1	3	1
	OPTIONAL	3	0	0	0
Cholesterol	DAY 1	8	5	10	15
	DAY 2	9	4	5	20

(CONTINUED)

APPENDIX A.3.2
Summary of Change from Baseline in Blood Chemistry Parameters

PARAMETER	VISIT	BASELINE/OBSERVATION			
		NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
Cholesterol	DAY 3	10	3	5	21
	DAY 7	7	4	3	22
	OPTIONAL	0	0	2	1
Creatinine	DAY 1	35	1	1	2
	DAY 2	34	2	3	0
	DAY 3	35	2	3	0
	DAY 7	31	2	2	1
	OPTIONAL	2	2	0	1
Direct Bilirubi	DAY 1	16	0	0	0
	DAY 2	16	1	0	0
	DAY 3	18	0	0	0
	DAY 7	19	0	0	0
	OPTIONAL	2	0	0	0
Glucose	DAY 1	28	3	1	6
	DAY 2	28	3	2	5
	DAY 3	27	5	1	6
	DAY 7	25	3	2	5
	OPTIONAL	1	1	0	1
LDH	DAY 1	29	5	3	2
	DAY 2	27	6	1	3
	DAY 3	30	3	3	2
	DAY 7	27	3	2	3
	OPTIONAL	3	1	0	1
Phosphorus	DAY 1	34	3	1	0
	DAY 2	34	2	1	0
	DAY 3	34	3	1	0
	DAY 7	31	3	1	0
	OPTIONAL	1	1	1	0
Potassium	DAY 1	32	1	4	1
	DAY 2	31	3	4	0
	DAY 3	30	4	4	1
	DAY 7	29	1	3	2
	OPTIONAL	3	0	0	0
Sodium	DAY 1	36	2	1	0
	DAY 2	35	3	1	0
	DAY 3	37	2	1	0
	DAY 7	33	2	1	0
	OPTIONAL	2	3	0	0
Total Bilirubin	DAY 1	34	0	0	3
	DAY 2	34	0	2	1
	DAY 3	37	0	0	3
	DAY 7	34	0	2	

(CONTINUED)

APPENDIX A.3.2
Summary of Change from Baseline in Blood Chemistry Parameters

PARAMETER	VISIT	BASELINE/OBSERVATION			
		NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
Total Bilirubin	OPTIONAL	6	0	0	0
Total Protein	DAY 1	22	10	2	4
	DAY 2	23	8	3	3
	DAY 3	24	6	5	1
	DAY 7	29	0	2	4
	OPTIONAL	1	2	1	2
Triglycerides	DAY 1	17	3	4	7
	DAY 2	18	2	3	9
	DAY 3	17	3	2	10
	DAY 7	17	2	5	6
	OPTIONAL	1	0	0	2
Uric Acid	DAY 1	37	0	1	1
	DAY 2	35	1	1	1
	DAY 3	34	3	1	1
	DAY 7	28	3	2	0
	OPTIONAL	3	2	0	0

APPENDIX A.3.3
Change From Baseline In Urinalysis Parameters

PARAMETER	VISIT	BASELINE/OBSERVATION			
		NORMAL/NORMAL	NORMAL/ABNORMAL	ABNORMAL/NORMAL	ABNORMAL/ABNORMAL
Specific Gravit	DAY 1	33	3	1	0
	DAY 2	32	1	1	0
	DAY 3	36	1	1	0
	DAY 7	28	2	1	0
pH	DAY 1	33	3	1	0
	DAY 2	33	1	1	0
	DAY 3	36	1	0	0
	DAY 7	29	1	0	0

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

BPD 001

APPENDIX A.4

15:51 Wednesday, June 23, 1999

SUMMARY OF ALL ADVERSE EVENTS BY BODY SYSTEM, SEVERITY AND RELATIONSHIP

COSTART BODY SYSTEM adverse events	PATIENTS		No. OF EVENTS	SEVERITY				RELATED TO TREATMENT	
	N	(%)		MILD	MODERATE	SEVERE	UNKNOWN	PATIENTS N (%)	EVENTS
BODY AS A WHOLE	19	(54)	49						
asthenia	6	(17)	7	2	4	1	0	0 (0)	0
headache	6	(17)	7	3	3	1	0	0 (0)	0
fever	6	(17)	6	5	1	0	0	2 (6)	2
pain	6	(17)	6	3	1	2	0	3 (9)	3
death	4	(11)	4	0	0	4	0	1 (3)	1
face edema	3	(9)	3	0	2	1	0	3 (9)	3
malaise	3	(9)	3	3	0	0	0	1 (3)	1
abdominal pain	2	(6)	2	0	2	0	0	0 (0)	0
back pain	2	(6)	2	0	1	1	0	0 (0)	0
infection	2	(6)	2	2	0	0	0	0 (0)	0
neck pain	2	(6)	2	1	1	0	0	0 (0)	0
abscess	1	(3)	1	1	0	0	0	0 (0)	0
chest pain	1	(3)	1	1	0	0	0	1 (3)	1
chills	1	(3)	1	1	0	0	0	0 (0)	0
flu syndrome	1	(3)	1	1	0	0	0	0 (0)	0
injection site reaction	1	(3)	1	1	0	0	0	0 (0)	0
CARDIOVASCULAR	11	(31)	14						
vasodilatation	5	(14)	6	6	0	0	0	1 (3)	1
hypertension	3	(9)	3	2	0	1	0	1 (3)	1
tachycardia	2	(6)	2	1	1	0	0	0 (0)	0
atrial fibrillation	1	(3)	1	0	1	0	0	0 (0)	0
hypotension	1	(3)	1	0	0	1	0	0 (0)	0
migraine	1	(3)	1	0	1	0	0	0 (0)	0
DIGESTIVE	13	(37)	23						
nausea	8	(23)	9	8	1	0	0	2 (6)	2
vomiting	6	(17)	6	4	2	0	0	2 (6)	2
anorexia	2	(6)	2	0	2	0	0	0 (0)	0
diarrhea	2	(6)	2	1	1	0	0	0 (0)	0
dyspepsia	1	(3)	1	1	0	0	0	0 (0)	0
gingivitis	1	(3)	1	1	0	0	0	0 (0)	0
hepatitis	1	(3)	1	0	0	1	0	1 (3)	1
liver function test abnormal	1	(3)	1	0	0	0	1	0 (0)	0
HEMIC & LYMPHATIC	11	(31)	19						
leukopenia	6	(17)	8	4	2	1	1	0 (0)	0
hypochromic anemia	2	(6)	3	3	0	0	0	1 (3)	1
reticulocytopenia	2	(6)	2	2	0	0	0	0 (0)	0
anemia	1	(3)	2	0	2	0	0	0 (0)	0
hemolysis	1	(3)	1	1	0	0	0	0 (0)	0
leukocytosis	1	(3)	1	1	0	0	0	1 (3)	1
lymphadenopathy	1	(3)	1	1	0	0	0	0 (0)	0
purpura	1	(3)	1	0	1	0	0	1 (3)	1
METABOLIC & NUTRITIONAL	15	(43)	26						
peripheral edema	6	(17)	6	3	1	2	0	3 (9)	3
hypercholesteremia	5	(14)	5	1	4	0	0	0 (0)	0
hyperlipemia	4	(11)	4	2	2	0	0	0 (0)	0
hyperglycemia	3	(9)	3	1	1	1	0	0 (0)	0
weight loss	3	(9)	3	0	1	0	2	0 (0)	0
bilirubinemia	2	(6)	2	2	0	0	0	0 (0)	0
albuminuria	1	(3)	1	1	0	0	0	0 (0)	0
edema	1	(3)	1	0	1	0	0	1 (3)	1
sgpt increased	1	(3)	1	1	0	0	0	0 (0)	0
MUSCULOSKELETAL	5	(14)	6						
myasthenia	2	(6)	2	1	0	0	1	0 (0)	0

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APPENDIX A.4

15:51 Wednesday, June 23, 1999

SUMMARY OF ALL ADVERSE EVENTS BY BODY SYSTEM, SEVERITY AND RELATIONSHIP

COSTART BODY SYSTEM adverse events	PATIENTS		No. OF EVENTS	SEVERITY				RELATED TO TREATMENT		
	N	(%)		MILD	MODERATE	SEVERE	UNKNOWN	PATIENTS N (%)	EVENTS	
myalgia	1	(3)	2	0	2	0	0	0	(0)	0
arthralgia	1	(3)	1	0	0	1	0	0	(0)	0
bone pain	1	(3)	1	1	0	0	0	0	(0)	0
NERVOUS SYSTEM	11	(31)	21							
dizziness	6	(17)	7	6	1	0	0	0	(0)	0
paresthesia	2	(6)	3	3	0	0	0	0	(0)	0
anxiety	2	(6)	2	1	1	0	0	1	(3)	1
hypertonia	2	(6)	2	1	1	0	0	0	(0)	0
somnolence	2	(6)	2	2	0	0	0	0	(0)	0
amnesia	1	(3)	1	1	0	0	0	0	(0)	0
depression	1	(3)	1	1	0	0	0	0	(0)	0
myoclonus	1	(3)	1	0	0	1	0	0	(0)	0
nystagmus	1	(3)	1	1	0	0	0	0	(0)	0
tremor	1	(3)	1	1	0	0	0	0	(0)	0
ONCOLOGY	4	(11)	5							
skin metastases	2	(6)	3	0	1	2	0	0	(0)	0
metastases	1	(3)	1	0	0	1	0	0	(0)	0
progressive disease	1	(3)	1	0	0	1	0	0	(0)	0
RESPIRATORY	9	(26)	18							
dyspnea	3	(9)	6	2	0	4	0	0	(0)	0
cough	3	(9)	4	4	0	0	0	0	(0)	0
lung disorder	2	(6)	2	1	0	1	0	0	(0)	0
rhinitis	2	(6)	2	1	1	0	0	0	(0)	0
asthma	1	(3)	1	1	0	0	0	1	(3)	1
pharyngitis	1	(3)	1	1	0	0	0	0	(0)	0
pleural effusion	1	(3)	1	0	1	0	0	0	(0)	0
pneumothorax	1	(3)	1	0	0	1	0	0	(0)	0
SKIN & APPENDAGES DERM ERY	7	(20)	8							
rash	6	(17)	7	7	0	0	0	0	(0)	0
exfoliative dermatitis	1	(3)	1	1	0	0	0	0	(0)	0
SKIN & APPENDAGES DERM HYP	1	(3)	1							
lichenoid dermatitis	1	(3)	1	1	0	0	0	0	(0)	0
SKIN & APPENDAGES GENERAL	5	(14)	5							
pruritus	4	(11)	4	3	0	1	0	2	(6)	2
skin disorder	1	(3)	1	1	0	0	0	0	(0)	0
SKIN & APPENDAGES HAIR	1	(3)	1							
alopecia	1	(3)	1	0	0	1	0	0	(0)	0
SKIN & APPENDAGES PIG	1	(3)	1							
leukoderma	1	(3)	1	1	0	0	0	0	(0)	0
SKIN & APPENDAGES SWEAT GLAND DISORDERS	3	(9)	3							
sweating	2	(6)	2	2	0	0	0	1	(3)	1
miliaria	1	(3)	1	1	0	0	0	0	(0)	0
SKIN & APPENDAGES TREATMENT SITES DURING LASER	26	(74)	68							
warmth	17	(49)	30	20	8	2	0	17	(49)	30
burning	8	(23)	9	8	1	0	0	8	(23)	9

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APPENDIX A.4

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SUMMARY OF ALL ADVERSE EVENTS BY BODY SYSTEM, SEVERITY AND RELATIONSHIP

COSTART BODY SYSTEM adverse events	PATIENTS N (%)	No. OF EVENTS	SEVERITY				RELATED TO TREATMENT	
			MILD	MODERATE	SEVERE	UNKNOWN	PATIENTS N (%)	EVENTS
pain	7 (20)	14	2	7	5	0	7 (20)	13
pruritus	6 (17)	6	6	0	0	0	6 (17)	6
tingling	2 (6)	3	3	0	0	0	2 (6)	3
prickling	1 (3)	3	2	1	0	0	1 (3)	3
discomfort	1 (3)	1	1	0	0	0	1 (3)	1
erythema	1 (3)	1	0	1	0	0	1 (3)	1
stinging	1 (3)	1	1	0	0	0	1 (3)	1
SKIN & APPENDAGES TREATMENT SITES AFTER LASER	28 (80)	192						
pain	20 (57)	42	20	19	3	0	20 (57)	42
edema	9 (26)	17	7	9	1	0	9 (26)	17
pruritus	8 (23)	13	11	2	0	0	7 (20)	12
erythema	7 (20)	19	8	11	0	0	7 (20)	19
tenderness	7 (20)	10	6	4	0	0	7 (20)	10
purpura	6 (17)	10	2	6	2	0	6 (17)	10
blanching	5 (14)	11	9	2	0	0	4 (11)	10
local eschar	4 (11)	18	2	10	6	0	4 (11)	18
warmth	4 (11)	6	6	0	0	0	4 (11)	6
skin necrosis	4 (11)	5	0	2	3	0	4 (11)	5
blister	3 (9)	5	2	3	0	0	3 (9)	5
skin discoloration	3 (9)	5	4	1	0	0	3 (9)	5
petechia	3 (9)	4	2	2	0	0	3 (9)	4
discomfort	3 (9)	3	3	0	0	0	3 (9)	3
stinging	3 (9)	3	2	1	0	0	3 (9)	3
scab	2 (6)	4	2	2	0	0	2 (6)	4
infection	2 (6)	3	3	0	0	0	0 (0)	0
tight skin	2 (6)	2	1	1	0	0	2 (6)	2
skin atrophy	1 (3)	2	2	0	0	0	1 (3)	2
skin hypertrophy	1 (3)	2	2	0	0	0	1 (3)	2
burning	1 (3)	1	1	0	0	0	1 (3)	1
dry skin	1 (3)	1	0	1	0	0	1 (3)	1
ecchymosis	1 (3)	1	1	0	0	0	1 (3)	1
healing abnormal	1 (3)	1	1	0	0	0	0 (0)	0
papule	1 (3)	1	1	0	0	0	0 (0)	0
pustule	1 (3)	1	0	1	0	0	1 (3)	1
serous discharge	1 (3)	1	1	0	0	0	1 (3)	1
skin ulcer	1 (3)	1	0	1	0	0	1 (3)	1
SPECIAL SENSES	10 (29)	17						
glare	3 (9)	3	3	0	0	0	2 (6)	2
amblyopia	2 (6)	3	3	0	0	0	1 (3)	1
vision abnormal	2 (6)	3	3	0	0	0	0 (0)	0
taste loss	2 (6)	2	2	0	0	0	0 (0)	0
ear pain	1 (3)	2	0	2	0	0	0 (0)	0
conjunctivitis	1 (3)	1	1	0	0	0	1 (3)	1
eye fatigue	1 (3)	1	1	0	0	0	0 (0)	0
eye pain	1 (3)	1	1	0	0	0	0 (0)	0
eye strain	1 (3)	1	1	0	0	0	1 (3)	1
UROGENITAL	7 (20)	19						
urine abnormality	5 (14)	11	8	3	0	0	0 (0)	0
hematuria	3 (9)	3	2	1	0	0	0 (0)	0
bacteriuria	2 (6)	2	2	0	0	0	0 (0)	0
glycosuria	1 (3)	1	0	1	0	0	0 (0)	0
urinary casts	1 (3)	1	1	0	0	0	0 (0)	0
vaginal hemorrhage	1 (3)	1	1	0	0	0	0 (0)	0

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APPENDIX C —Patient Capsule Summaries

C.1 Deaths

Patient 3

Patient 11

Patient 18

Patient 19

C.2 Withdrawals Due to an Adverse Event

No patient withdrew from Study BPD 001

C.3 Other Serious Adverse Events

Patient 13

CR-96013
Verteporfin for Injection

Clinical Study Report BPD 001
Cutaneous Oncology

C.1 Deaths
Patient 3
Patient 11
Patient 18
Patient 19

CAPSULE SUMMARY

(Page 1 of 1)

Study:	BPD 001	Event:	Death
Patient No.:	3	Relationship to Therapy:	Definitely Not
Inv.:	Anderson	Date of Event:	April 5, 1992
Site Name (No.):	Boston (1)	Study Day:	Day 110
Treatment:	verteporfin		

Patient 3 was a 65-year-old woman with cerebral and CNS metastases. The patient had Grave's disease and had a history of malignant left pleural effusion. She received radiotherapy between July 1991 and October 1991. Two months prior to PDT, the patient was on intralesional vinblastine for nodules on her back.

On December 17, 1991, the patient received 0.25 mg/kg of verteporfin and 50 J/cm² of light on three treatment fields (total of 6 tumors) located on her chest and right lower abdomen. The patient returned for her Day 95 visit, Four of her skin tumors were graded as SD (stable disease) and two were considered PD (progressive disease). Increasing peripheral lymphadenopathy following treatment preceded her death on April 5, 1992 (110 days after PDT). The patient's decline was not considered related to PDT treatment.

CAPSULE SUMMARY

(Page 1 of 1)

Study:	BPD 001	Event:	Death
Patient No.:	11	Relationship to Therapy:	Possibly Related
Inv.:	Anderson	Date of Event:	July 10, 1992
Site Name (No.):	Boston (1)	Study Day:	Day 81
Treatment:	verteporfin		

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 carcinoma on April 20, 1992. The last skin tumor assessment was performed 35 days after PDT, and the tumor was considered to be complete response.

Hospitalization due to deterioration of liver functions, as indicated by elevations in bilirubin, alanine, and aspartate aminotransferase levels, occurred 71 days post-dose. The patient died of bleeding esophageal varices 81 days post-dose. 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 veins, which could only be produced by long-standing liver disease.

CAPSULE SUMMARY

(Page 1 of 1)

Study:	BPD 001	Event:	Death
Patient No.:	18	Cause of Seriousness:	
Inv.:	Anderson	Relationship to Therapy:	Definitely Not
Site Name (No.):	Boston (1)	Date of Event:	December 22, 1992
Treatment:	verteporfin	Study Day:	Day 35

Patient 18 was a 76-year-old woman with metastatic disease. The patient was diabetic. She received radiation and chemotherapy in 1991. She received PDT (0.20 mg/kg and 150 J/cm² of light) on November 18, 1992.

The patient expired on December 22, 1992, due to respiratory arrest and progression of her underlying disease. An autopsy was not performed. Cause of death was judged by the Investigator to be not related to PDT.

CAPSULE SUMMARY

(Page 1 of 1)

Study:	BPD 001	Event:	Death
Patient No.:	29	Relationship to Therapy:	Remotely
Inv.:	Lui	Date of Event:	August 18, 1994
Site Name (No.):	2	Study Day:	Day 59
Treatment:	verteporfin		

Patient 29 was a 69-year-old woman with breast cancer. The patient was a heavy smoker and had a history of pneumonia. For her breast cancer, the patient received FAC Chemotherapy (between November 18, 1991 and January 1, 1992), radiation on her left breast (between January 30, 1992 and February 2, 1992), and a second course of FAC Chemotherapy (between March 2, 1992 and May 4, 1992). She was on tamoxifen between June of 1992 and June 8, 1994. The patient had multiple cutaneous nodules and clinically enlarged peripheral lymph nodes prior to PDT.

On June 20, 1994, the patient received PDT (0.30 mg/kg of verteporfin and 25 - 50 J/cm² of light) on three treatment fields. She was hospitalized on four occasions (June 27, 1994 - July 2, 1994; July 10-14 1994; July 19-28, 1994; and July 31-August 18, 1994) following PDT for management of symptomatic pleural effusions with repeat thoracenteses. The patient died on August 18, 1994. Permission for an autopsy was not granted by the family. The Investigator reported that her death was due to progression of underlying disease.

C.2 Withdrawals Due to an Adverse Event

No patient withdrew due to Adverse Events from Study BPD 001

C.3 Other Serious Adverse Events
Patient 13

CAPSULE SUMMARY

(Page 1 of 1)

Study:	BPD 001	Event:	Associated Serious Event
Patient No.:	13	Relationship to Therapy:	Possibly Related
Inv.:	Lui	Date of Event:	May 6, 1992
Site Name (No.):	2	Study Day:	Day 28
Treatment:	verteporfin		

Patient 13 was a 53-year-old man with Bowen's disease and cutaneous metastatic lesions. On May 6, 1992, 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 on the same leg that was treated with PDT. Edema of this 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 post-treatment. 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.

The patient returned for his Day 7, 14, 21, and 28 follow-up visits. On his last visit, CR_T was recorded for all the treated tumors. The patient withdrew to receive alternative therapy (chemotherapy) after Day 28 for new lesions occurring outside the treatment fields.

Clinical Study Report — BPD 002

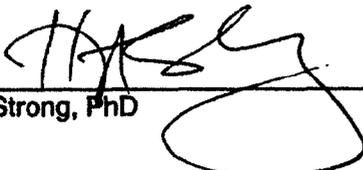
Verteporfin for Injection

**A Phase I/II Photodynamic Therapy Study for the
Evaluation of Intravenous BPD-MA in the
Treatment of Psoriasis**

May 21, 1999

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

Study Clinical Director:



Andrew Strong, PhD

May 21 1999.
Date

Study Statistician:



Xiang Yao Su, PhD

May 21, 1999
Date

Study Medical Writer:



Michael Weaver, PhD

May 21, 1999
Date

This study was conducted in accordance with the guidelines in "Ethics in Human Experimentation", medical research report #6, Canada 1978 and in US 21 CFR, part 50.25.

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

QUALITY ASSURANCE REVIEW STATEMENT

Study Number and Title: BPD 002, A Phase I/II Photodynamic Therapy Study for the Evaluation of Intravenous BPD-MA in the Treatment of Psoriasis

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

May 21/99
Date

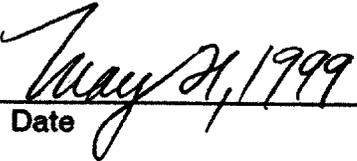
APPROVAL STATEMENT

This Clinical Study Report of Study BPD 002, entitled "A Phase I/II Photodynamic Therapy Study for the Evaluation of Intravenous BPD-MA in the Treatment of Psoriasis" is approved as an accurate record of the conduct and results of the study.

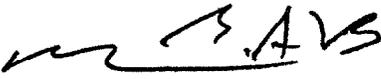
Approved by:



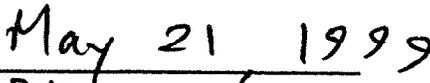
Noel Buskard, MD, FRCP, FACP
Safety and Medical Officer



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 monoacids A ring)		
Study Number and Title:	BPD 002: A Phase I/II Study for the Evaluation of Intravenous Verteporfin in the Treatment of Psoriasis	
Study Investigator(s) and Center(s):	Harvey Lui, MD (Vancouver, Canada): Principal Investigator Rox Anderson, MD (Boston, USA) Luciann Hruza, MD (St. Louis, USA)	
Date of First Patient Enrolled:	December 28, 1992	
Date of Last Patient Enrolled:	October 14, 1994	
Date of Last Patient Completed:	January 10, 1995	Clinical Phase: Phase I/II
Study Objective(s):	<ol style="list-style-type: none"> 1. To determine the minimum drug and light dose combination that provides evidence of a clinical response and is shown to be safe in the treatment of psoriasis. 2. To obtain information on the safety and efficacy of a light-emitting diode (LED) light source compared to a laser light source in the treatment of psoriasis. 3. To obtain preliminary information about the distribution of verteporfin in skin. 	
Study Description (Methods and Investigational Plan):		
Design	Phase I/II, three-center, non-randomized, open-label study to evaluate the efficacy and safety of photodynamic therapy (PDT) using a single dose of intravenous verteporfin and various doses of either laser and LED light in psoriasis.	
Population	Patients who had moderate to severe, stable chronic plaque psoriasis for at least 12 months. This study planned to enroll a maximum of 36 patients. Other psoriasis medications were excluded for 1 month prior to enrollment and throughout the trial.	
Treatment (Identity of Investigational Products)	Verteporfin was provided as 25 mg vials of freeze-dried powder (Batch #R1186-192; R1186-102) Verteporfin was administered as a single 45-minute IV infusion at a dose of 0.2 mg/kg. Each patient had 7-9 distinct psoriasis plaque sites and 1-2 normal skin sites selected. One normal skin site acted as a drug and light-control, one plaque site acted as a light only control and a second plaque site acted as a drug-only control. Treatment sites were exposed to a different dose of either laser (690 ± 3 nm; 30 J/cm ² -80 J/cm ²) or LED (688 ± 10 nm; 25 J/cm ² -75 J/cm ²) light 3 hours after the start of the verteporfin infusion. The laser sources were supplied by Coherent Corporation. The LED panels were supplied by Quantum Devices Inc.	

<p>Study Description (Methods and Investigational Plan) (cont'd):</p> <p>Efficacy and Safety Variables</p> <p>Efficacy</p> <p>Safety</p> <p>Efficacy and Safety Assessments</p> <p>Efficacy</p> <p>Safety</p> <p>Statistical Methods</p> <p>Efficacy</p> <p>Safety</p>	<ul style="list-style-type: none"> • lesion response, the time to achieve a lesion response, and the time to recurrence in responding lesions. • the distribution of verteporfin in skin • adverse events, clinically significant changes in laboratory tests, vital signs, ophthalmic examinations, and test site reactions to PDT. <p>Lesion response was assessed by measuring plaque severity according to a 15-point severity scale on Days 0, 1, 2, 3, 7, 14, 21, 28, and 90.</p> <p>Accumulation of verteporfin in skin biopsy samples at various time points after drug infusion was to be measured using a spectrofluorometer.</p> <p>Adverse events were monitored in an ongoing fashion throughout the study. Test site reactions to PDT were assessed according to a 15-point scale on Days 0, 1, 2, 3, 7, 14, 21, 28, and 90. Laboratory tests were conducted at screening and on 1, 3, 7, and 28 days after the start of the verteporfin infusion. Ophthalmic and physical examinations were performed at screening and at a final 12-week follow-up visit after the verteporfin infusion. A pregnancy test was also performed, where applicable.</p> <p>Each treatment site was considered a separate experimental unit. A decrease in the plaque severity score compared to baseline (Day 0) of $\geq 25\%$ was defined as a response. Lesion response and recurrence were tabulated by drug and light dose at any evaluation day. The median number of days to a response and to a recurrence were estimated using the product-limit survival method. The measurement of verteporfin in the skin was not completed as planned.</p> <p>Adverse events were compiled and summarized by body system category, severity, and association with treatment. PDT-induced skin reactions were tabulated by the highest grade of reaction. All other safety data were listed.</p>
<p>Study Results:</p> <p>Patient Disposition and Demography</p> <p>Protocol Deviations</p> <p>Efficacy Results</p>	<p>A total of 21 patients were enrolled and all completed the study. The study population included 18 men and 3 women. The mean age was 50 ± 16 years. The average age at onset of psoriasis symptoms in these patients was 27.3 ± 14.0 years. The patients were of Skin Types II and III (on a scale from 1-6).</p> <p>None of the 21 patients developed withdrawal criteria during the study and none were withdrawn for any reason. No data were excluded due to protocol deviations.</p> <p>Overall, 68% of the treatment sites exhibited a response to treatment. The response rate in control sites was 51%. The median time to a response was 21 days. Of the lesions that responded, 65% recurred with a median time to recurrence of 50 days. The response rate appeared to be related to both the drug dose and light exposure. The highest response rates (irrespective of PDT-induced skin reactions) were observed in patients who received the 0.20 mg/kg dose of verteporfin and light doses of $\geq 30 \text{ J/cm}^2$.</p>

LIST OF ABBREVIATIONS

ALT	Alanine transferase
AST	Aspartate transaminase
BPD-MA	Benzoporphyrin derivative monoacids A ring (verteporfin)
BUN	Blood urea nitrogen
cm ²	square centimeter
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms Dictionary
CRO	Contract Research Organization
CS1	Control site 1
GGT	γ Glutamyltransferase
HDL	High density lipoprotein
HPD	Hematoporphyrin derivative
IRB	Institutional review board
J	joules
Kg	kilogram
LED	light-emitting diode
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
mg	milligrams
mW	milliWatts
PDT	photodynamic therapy
PUVA	Psoralen and ultraviolet A light therapy
RBC	Red blood cell count
SD	Standard deviation
TS1	Treatment site 1
UV	Ultraviolet electromagnetic radiation with wavelengths between 200-400 nm
UVA	Ultraviolet light with wavelengths between 320 and 400 nm
UVB	Ultraviolet light with wavelengths between 290 and 320 nm
WBC	White blood cell count

1. INTRODUCTION

Psoriasis is a chronic skin disorder characterized by epidermal hyperproliferation and dermal inflammation of unknown etiology. This condition affects approximately 2% of the world's population. Topical treatments such as corticosteroids, tar, anthralin, calcipotriol (e.g. Dovonex, a vitamin D3 derivative), and retinoids (eg. Tazorac™) are generally used for treating mild psoriasis (1). Phototherapy with ultraviolet-B light (UVB) or photochemotherapy using a combination of psoralen and ultraviolet-A light (PUVA) are used for patients with moderate to severe psoriasis. Immunosuppressive drugs such as cyclosporine and methotrexate are effective, but are generally reserved for treating more severe psoriasis. Standard therapy usually involves multiple treatments with different agents. Up to 30 treatment courses of ultraviolet therapy or several months of topical or systemic therapy may be required to achieve a remission.

Photodynamic therapy (PDT) is a two-step process consisting of treatment with a photosensitizer (light-activated drug) followed by nonthermal light. The light sources most commonly used are lasers and light-emitting diodes (LEDs). After exposure to light at a wavelength near the absorption peak of the photosensitizer, the photosensitizer undergoes an energy transition, culminating in the formation of singlet oxygen and intracellular free-radicals. These disrupt cellular structures such as the cell membrane, mitochondria, and lysosomal membranes and ultimately lead to death of the cell.

PDT using PHOTOFRIN® has been approved in several jurisdictions for treating malignancies of the bladder, esophagus, and lung. It has also been used experimentally to treat psoriasis and skin cancer. In psoriasis, plaque improvement has been shown in patients who were treated with PHOTOFRIN® or hematoporphyrin derivative (HPD) in combination with localized red or multiple whole-body UVA light exposures (2,3). Although therapeutic activity could be demonstrated in these studies, further work was discontinued in favor of a newer photosensitizer, verteporfin.

Verteporfin (benzoporphyrin derivative monoacids A ring, BPD-MA) is a second-generation photosensitizing molecule. Verteporfin for Injection is the lipid-based product, which is administered intravenously. Throughout this report Verteporfin for Injection will be referred to simply as verteporfin. Verteporfin preferentially accumulates in tumors, hyperproliferative tissues, and dividing lymphocytes and it can be activated by red light (highest absorption peak at 690 nm). Depending on the dose, the photosensitivity period in patients who have received verteporfin is relatively short (2-7 days).

Clinical Study BPD 002 was a dose-finding study of verteporfin and light in patients with psoriasis. The objective of the trial was to determine the lowest effective combination of verteporfin dose and light dose that could be safely administered to psoriasis patients.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Principal Investigator's Signature Page: Appendix D.3
List of Investigators and CVs: Appendix D.4

Country	Investigator	Study Center	Number of Patients Enrolled
Canada	Harvey Lui, MD Principal Investigator	Vancouver General Hospital Vancouver, BC	11
	David MacLean, MD Vincent Ho, MD Coinvestigators		
USA	Rox Anderson, MD Investigator	Wellman Laboratories of Photomedicine Massachusetts General Hospital Boston, MA	8
	Luciann Hruza, MD Investigator	Barnes West County Hospital St. Louis, MO	2

A curriculum vitae of each investigator is provided in Appendix D.4.

This study was sponsored by QLT PhotoTherapeutics Inc. (QLT) of Vancouver, Canada. In the protocol dated December 7, 1992, QLT and a contract research organization (CRO) National Medical Research Corporation Inc. (NMRC) were jointly responsible for managing and monitoring this trial. QLT and NMRC ensured that the Investigator and their staff adhered to the protocol, completed the Case Report Form properly, and maintained adequate source documentation. During the study, the CRO was changed to Integrated Research Inc. (IRI) of Ste. Laurent, Quebec.

QLT was also responsible for supply chain management and data analysis throughout the study. The study clinical director was H. Andrew Strong, PhD. Statistical analysis was provided by Xiang Yao Su, PhD. The study monitors were Annette Mesquita, MSc and Ling Wu, MSc, MD. Kelly Smith was responsible for supply chain management.

In an amendment dated April 11, 1994, the responsibilities of the CRO for managing and monitoring the trial were assumed by QLT.

Contract Research Services

National Medical Research Corporation
25 Main Street
Hartford, CT 06106

Integrated Research Inc.
485 Boulevard Decarie
Ste. Laurent, Quebec

3. STUDY ETHICAL CONSIDERATIONS

3.1 Institutional Review Board (IRB)

IRB Approvals: Appendix D.5.1

The protocol and corresponding Informed Consent form were reviewed, and the experimental procedures found to be acceptable on ethical grounds for research involving human patients at each of the study sites.

3.2 Ethical Conduct of the Study

This study was conducted in accordance with the guidelines in "Ethics in Human Experimentation", medical research report #6, Canada 1978 and in US 21 CFR, part 50.25.

3.3 Patient Information and Consent

Sample Patient Information and Consent Form: Appendix D.5.2

The Investigator or his/her delegate explained full details of this protocol and the study procedure to potential patients prior to study enrollment. Benefits and risks resulting from participation in this study were also explained to each potential patient. Participants were advised that they were free to withdraw from the study at any time, without compromising their medical care. All patients read and signed an appropriate Institutional Review Board (IRB)-approved consent form, indicating their consent to participate in this study. A sample of the informed consent form at each center is provided in Appendix D.5.2.

4. STUDY OBJECTIVES

1. To determine the minimum drug and light dose combination that provides evidence of a clinical response and is shown to be safe in the treatment of psoriasis.
2. To obtain preliminary information on the distribution of BPD-MA (verteporfin) in skin.

In an amendment dated 11 April, 1994, a third objective was added:

3. To obtain information on the safety and efficacy of a light-emitting diode (LED) light source compared with a laser light source in the treatment of psoriasis.

5. STUDY DESCRIPTION (METHODS AND INVESTIGATIONAL PLAN)

Protocol and Protocol Amendments: Appendix D.1
Sample Case Report Form: Appendix D.2

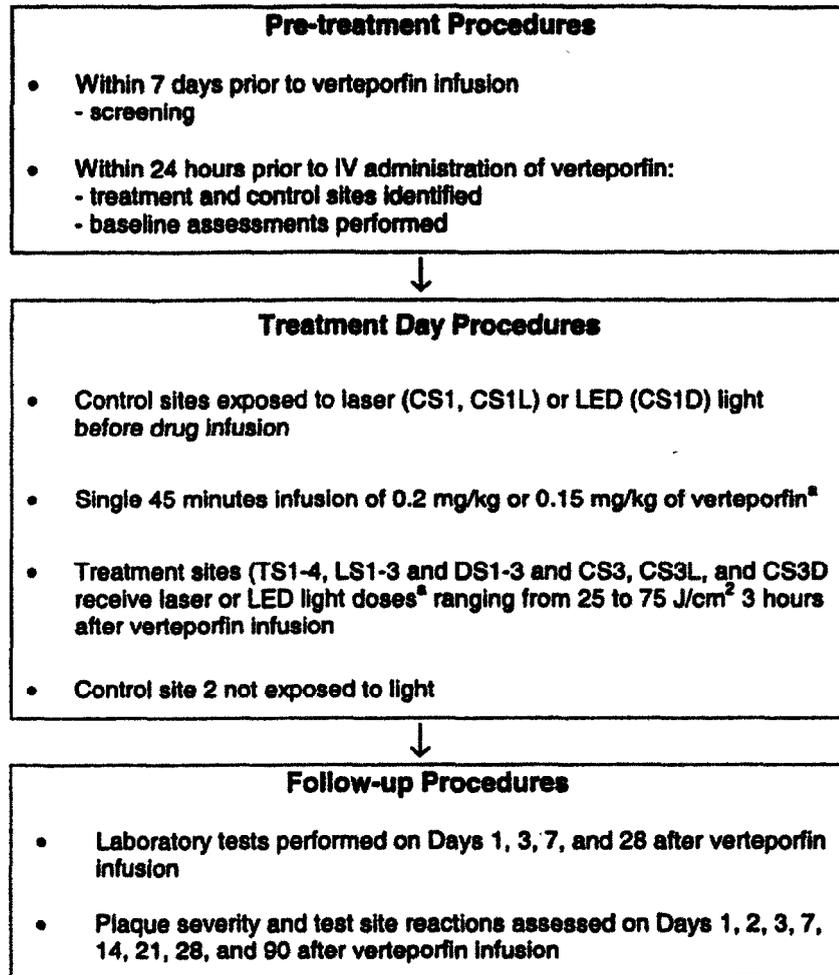
5.1 Overall Study Design

Study BPD 002 was a Phase I/II nonrandomized, open-label study that evaluated the safety and potential efficacy of photodynamic therapy (PDT) in treating small areas of plaque in patients with chronic psoriasis vulgaris. In Part A of the study, patients received a single intravenous infusion of verteporfin followed by exposure to nonthermal red light (i.e. laser) at a wavelength of 690 nm to activate the drug.

The dose of verteporfin used was based upon the results of a preceding study, Study BPD 001, which assessed the safety and potential efficacy of a range of doses of verteporfin in a Phase I/II trial in patients with cutaneous cancer (4). In that trial, a drug and light dose combination of 0.15 mg/kg of drug and 150 J/cm² of light or 0.25 mg/kg of drug and 50 J/cm² of light produced a clinical response in superficial tumors with acceptable reactions in the peritumoral area.

Treatment was administered on an outpatient basis. The initial drug dose was to be 0.20 mg/kg followed by light doses ranging from 25 J/cm² to 75 J/cm². Light was to be applied 3 hours after the start of the drug infusion. If clinical responses and/or significant local toxicity occurred in the first 3 patients, the dose of verteporfin and light was to be adjusted according to criteria defined in the protocol and its amendments.

The protocol was dated December 7, 1992 and it was amended on 3 subsequent occasions that are summarized in Section 5.8.1. In an amendment dated April 11, 1994, the treatment schedule was modified to include an LED light source (688 ±10 nm) in addition to the laser light source. The laser treatment schedule described in the earlier versions of the protocol was redefined as Part A. The amended treatment schedule that included both the laser and LED light sources was designated as Part B. The study design is illustrated in Flow Chart 1 below.



^a Actual drug and light doses were to be determined from the results from the first 3 patients.

FLOW CHART 1. Study Design

5.2 Study Population

To be eligible for this study, patients were required to have moderate to severe chronic, stable plaque psoriasis. This condition must have been present for at least 12 months prior to study entry. Men and women were eligible for enrollment.

5.2.1 Number of Patients

In the original protocol, a minimum of 12 patients were to be enrolled in 2 study centers. In Part B, a minimum of 12 additional patients were to be enrolled and a third study center

(Dr. Hruza, St. Louis) was added. In an amendment dated July 19, 1994, the sample size was increased to a maximum of 36 patients overall (24 in Part A and 12 in Part B).

5.2.2 Inclusion Criteria

1. Chronic, stable plaque psoriasis with disease present for at least 12 months. Treatment lesions were not to be located on the face, scalp, palms, soles, and on the lower 1/3 of the legs, fingers, and intertriginous areas. The area of involved skin was to be sufficient to allow for the number of sites described in Sections 5.3.1.2(a).
2. Each site was to have a minimum plaque severity score of 8.0 as described in Section 5.5.1.
3. At least 18 years of age.
4. Male or female. Female patients must have either have been postmenopausal with a negative serum pregnancy test or surgically sterile. In an amendment dated July 19, 1994, this criterion was changed to include non-nursing females who were using a medically acceptable form of birth control that, in the opinion of the Investigator, would be readily maintained during treatment with verteporfin. All female patients using active birth control methods were required to have a negative serum pregnancy test within one week of study entry.
5. Patient read, understood, and signed the consent form.

5.2.3 Exclusion Criteria

1. Prior use of PHOTOFRIN® (porfimer sodium) or verteporfin.
2. Use of topical corticosteroids, emollients, keratolytics; tar preparations, anthralin, or salicylic acid to treatment lesion in the 2 weeks before study entry.
3. Use of any photosensitive drug (phenothiazine, tetracycline, etc.) in the month before study entry.
4. Use of systemic glucocorticoid therapy or long-term therapy with NSAID's in the month before study entry.
5. Use of psoralen phototherapy or PUVA within 2 months of study entry.
6. Use of any investigational drug within 2 months of study entry.
7. Use of cyclosporine or methotrexate therapy within 3 months of study entry.

8. Use of retinoid therapy within 6 months of study entry.
9. Pustular, guttate, or erythrodermic psoriasis, acute flaring psoriasis, or psoriasis covering over 30% of body surface area.
10. Porphyria, other porphyrin sensitivity, or hypersensitivity to bright light.
11. History of exacerbation of their psoriasis by sunlight.
12. Serious dermatological disease other than psoriasis in the area to be treated.
13. History of systemic lupus erythematosus, psoriatic, or rheumatoid arthritis.
14. Skin types V and VI (Table 5).
15. Serious ophthalmic disease (e.g. cataract, glaucoma).
16. History of drug or alcohol abuse, or patients whom the Investigator believed would not cooperate in completing this study.
17. Patient with clinically significant renal, metabolic, cardiac, neurological, and gastrointestinal disease.
18. History of diffuse liver disease and/or abnormal liver function tests at baseline (including GGT).
19. Patients with a history of serious immunodeficiency disorders.
20. Uncontrolled hypertension (blood pressure $\geq 140/95$).
21. Patients with a fever or any acute illness not explained by an underlying condition.

In an amendment dated July 19, 1994, patients with active nonsuperficial thrombophlebitis were also excluded. This amendment was requested the Health Canada for patients who were enrolled in the Canadian center.

5.2.4 Removal of Patients From Treatment and/or Assessments

The Sponsors retained the right to remove any study patient whose welfare, in the opinion of the Investigator or Medical Director, would be compromised by further participation in this study. Reasons for doing so included intercurrent illness, development of a severe adverse event or a clinically significant laboratory abnormality. Patients had the right to withdraw from the study at any time for any reason. Noncompliance with the study treatments or

restrictions would also have been considered cause for withdrawing a patient from further study.

5.2.5 Special Restrictions

Patients were advised to stay indoors during daylight hours, to protect their eyes and skin from direct sunlight and strong artificial sources and that they might remain photosensitive for 3 days, irrespective of using sunscreens. In the amendment dated April 11, 1994, the period during which patients were to be protected from light was increased to 7 days. They were also advised that they should not avoid normal light completely, as photobleaching of the drug due to exposure to low light may be important in decreasing the period of skin photosensitivity. They were cautioned to avoid cone or helmet style hair dryers as concentrated heat from these sources has been associated with a photosensitivity-like reaction accompanied by erythema and induration in some patients treated with PHOTOFRIN®, which is a hematoporphyrin-based photosensitizer also used in PDT.

The following general eye precautions were recommended for at least 3 months after treatment:

- Wearing sunglasses with an average luminance transmittance of about 4% and minimal transmittance of ultraviolet radiation (<1%) both in sunlight and in brightly illuminated indoor environments.
- Avoiding ophthalmic examinations such as direct and indirect ophthalmoscopy, slit-lamp biomicroscopy, etc. that utilize bright light.

5.3 Study Treatments

5.3.1 Verteporfin PDT

PDT was administered as a two-step process, the first being infusion of verteporfin at a dose of 0.2 mg/kg. The second step was activation of verteporfin by illumination with red light from a laser (690 ±3 nm) or an LED (688±10 nm) source.

5.3.1.1 Verteporfin Infusion

The initial dose of verteporfin used in study BPD 002 was 0.20 mg/kg, given as a single intravenous infusion over a 45-minute period. The dose was to be adjusted according to criteria set out in the protocol as described in Section 5.3.1.4.

The drug was supplied in clear glass vials of 25 mg of verteporfin as a freeze-dried powder. The verteporfin powder was reconstituted to produce a final concentration of 2.0 mg/mL.

Full reconstitution and infusion instructions are provided in the protocol. After reconstitution, the vial(s) were placed in their original carton to protect them from light and they were used within 4 hours. Any unused portion of the reconstituted drug was discarded.

5.3.1.2 Light Administration

Device Information: Appendix D.7

The following light sources and doses were used to activate verteporfin:

Laser

In Part A, a 20 W argon-ion pumped-dye laser was used as the source of 690 ± 3 nm light. Laser light was delivered through a microlens fiber that was sterilized before use. A new fiber was used for each patient. The fiber was coupled to the laser tube via a laser-to-fiber optic delivery system. The initial light dose to be applied to the treatment sites was $25\text{-}75 \text{ J/cm}^2$ at a light intensity (power density) of 60 mW/cm^2 . The light dose schedule was modified by an amendment (Amendment 2) so that initial light doses were to be $30\text{-}60 \text{ J/cm}^2$.

LED

In Part B of the study, a 7×9 cm LED panel (688 ± 10 nm) was used in addition to the laser source as described in Amendment 2. The LED panel was positioned at a distance from the treatment or control skin site so that it delivered a light intensity of 60 mW/cm^2 . The exact distance between the skin sites and the LED light panel was determined by calibrating the LED light panel with a radiometer immediately before each treatment. An opaque template was used to mask surrounding tissues from stray light. The initial light dose applied to the treatment sites was to be $30\text{-}60 \text{ J/cm}^2$.

5.3.1.3 Selection of Treatment and Control Sites

a) Part A

The test sites for this study were areas of psoriasis plaque and normal skin that were selected by the Investigator. Psoriasis plaque sites were divided into control sites (CS), that either did not receive light or that received light before drug infusion, and treatment sites (TS) that received both drug and light. All sites were to be 1.8 cm in diameter and they were located at least 0.4 cm apart. The identity of these test sites is presented in Table 1 below.

TABLE 1. Selection of Test Sites and Laser Light Dose Schedule in Part A

Skin Site	Designation	Description	Laser Light Dose^a (J/cm²)
Control site 1	CS1	Psoriasis plaque	75 ^b
Control site 2	CS2	Psoriasis plaque	None
Control site 3	CS3	Normal skin	75
Treatment site 1	TS1	Psoriasis plaque	25
Treatment site 2	TS2	Psoriasis plaque	50
Treatment site 3	TS3	Psoriasis plaque	75
Treatment site 4 ^c	TS4	Psoriasis plaque	25 or 50 ^c

^a Delivered at an intensity of 80 mW/cm²

^b Light administered before drug infusion

^c According to the protocol amendment dated May 17, 1993

The treatment sites were areas of psoriasis plaque that received a complete course of PDT (i.e. both drug and light). Two additional plaque sites served as PDT control sites: control site 1 (CS1) was exposed to light before verteporfin infusion and control site 2 (CS2) was not exposed to light at any time. The third control site (CS3) was an area of normal skin that received 75 J/cm² of light. In an amendment dated May 17, 1993, an additional treatment site up to 5 cm in diameter (TS4) was added to the protocol. TS4 was to receive a light dose of 25 J/cm². If there was no response at this light dose in the first 3 patients, then the light dose was to be increased to 50 J/cm².

With the exception of CS1 and CS2, all other sites were exposed to laser light 3 hours after the start of the drug infusion according to the schedule in Table 1.

b) Part B

In Part B of the study, the number of plaque sites was increased from 6 per patient to 9 and the number of normal skin sites was increased from 1 to 2. All plaque sites were to be 1.8 cm across as in the original protocol. The identity of the treatment and control sites and the light dose schedule used in Part B of the study are presented in Table 2 below.

TABLE 2. Selection of Test Sites and Laser and LED Light Dose Schedule in Part B

Skin Site	Designation	Description	Light Source	Light Dose^a (J/cm²)
Control site 1	CS1D	Psoriasis plaque	LED	60 ^b
Control site 1	CS1L	Psoriasis plaque	Laser	60 ^b
Control site 2	CS2	Psoriasis plaque	None	None
Control site 3	CS3D	Normal skin	LED	60
Control site 3	CS3L	Normal skin	Laser	60
Laser site 1	LS1	Psoriasis plaque	Laser	30
Laser site 2	LS2	Psoriasis plaque	Laser	45
Laser site 3	LS3	Psoriasis plaque	Laser	60
Diode site 1	DS1	Psoriasis plaque	LED	30
Diode site 2	DS2	Psoriasis plaque	LED	45
Diode site 3	DS3	Psoriasis plaque	LED	60

^a Delivered at an intensity of 60 mW/cm²

^b Light administered prior to drug infusion

Six of the 9 psoriasis sites were designated as treatment sites: three of them were to be treated with laser light (LS1-LS3) and three were to be treated with LED light (DS1-DS3). Ideally, the laser and LED treatment sites were to be located on different sides of the body but in an equivalent location (e.g. left and right arms). The remaining three psoriasis plaque sites were PDT control sites. CS1D and CS1L were to be exposed to either laser (L) or LED (D) light before verteporfin infusion. CS2 was not exposed to light at any time. Two normal skin sites (CS3D and CS3L) served as controls for the LED and laser light, respectively.

With the exception of CS1D, CS1L, and CS2, all other sites were exposed to laser or LED light 3 hours after the start of the drug infusion according to the schedule in Table 3.

5.3.1.4 Criteria for Optimizing the Dose of Verteporfin and Light

a) Part A

The first six patients in Part A were to receive 0.20 mg/kg of verteporfin. The dose of verteporfin was thereafter to be increased or decreased as follows:

- If 3 or more patients exhibited a clinical response ($\geq 25\%$ decrease in lesion severity) one week after treatment, then the dose of verteporfin was to be

decreased to 0.15 mg/kg in subsequent patients. If fewer than 3 patients exhibited a clinical response, then the dose of verteporfin was to be increased to 0.25 mg/kg.

- If significant local toxicity (phototoxicity), defined as Grade 3 or higher skin toxicity (see Table 7 for skin reaction grading system) in the treated area, was observed at a light dose of 75 J/m², then this light dose was to be discontinued in subsequent patients. If Grade-3 phototoxicity developed at a light dose of 25 or 50 J/cm² then the verteporfin dose was to be reduced to 0.15 mg/kg. If Grade-3 phototoxicity was still evident, then the verteporfin dose was to be further reduced to 0.10 mg/kg. If it was not possible to use a light dose of 75 J/cm² at the 0.15 or 0.10 mg/kg dose of verteporfin, then this light dose was to be discontinued for the remainder of the study.

In the amendment dated April 11, 1994 the definition of significant phototoxicity was changed from Grade 3 or higher to Grade 4.

b) Part B

In Part B, at least 12 patients were to be treated with a fixed dose of 0.20 mg/kg of verteporfin. The initial light doses were to be 30, 45, and 60 J/cm². In the amendment dated July 19, 1994, the light dose was to be reduced by 15 J/cm² if any 2 patients developed a Grade-4 skin reaction at either the laser or LED sites.

5.3.2 Identity of Investigational Products

5.3.2.1 Verteporfin

Verteporfin is a semisynthetic derivative of hematoporphyrin. It has a maximum light absorption peak near 690 nm. The drug was supplied in clear glass vials of 25 mg of verteporfin as a freeze-dried powder. Two batches of verteporfin were used in the study. The first batch (R1186-192) was used by all three centers. A second batch (R1186-102) was used only in Vancouver.

5.3.2.2 Light Delivery Devices

The argon ion pumped dye lasers used in this study were supplied by Coherent Corporation. This was a commercially available laser with a 20 W power output and a wavelength of 690 ± 3 nm.

The LED panels were supplied by Quantum Devices Inc. (WI, USA). The LED panel had a central wavelength of 688 ± 10 nm, with a full-width half-maximum bandwidth of between 15 nm and 40 nm. The variation in light intensity across the area of skin to be treated was approximately 20%.

A listing of the devices used to deliver red light for PDT at each center is provided in Appendix D.7.

5.3.3 Assignment to Treatment

This was a Phase I/II, uncontrolled open label, dose-finding study. All patients who entered this trial were to receive a single infusion of verteporfin followed by LED or laser light. The verteporfin and light doses were to be adjusted according to efficacy and safety criteria described in Sections 5.3.1.3 and 5.3.1.4. The patient's identity was encoded on the Case Report Form.

5.3.4 Assessment of Treatment Compliance

All drug and light doses were administered under the supervision of study personnel. All infusion 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

Patients were required not to take any medications, including over-the-counter preparations for 10 days before and throughout the trial. The Investigator was to be promptly advised of any clinical symptoms that would require medication.

No concurrent therapies of any kind, including topical/systemic anti-bacterial agents, corticosteroids, or anti-histamines were allowed during the study without discussion and approval of the Medical/Clinical Monitor. All concomitant medications and the reasons for their use were recorded on each patient's Case Report Form.

5.4 Study Procedures

The schedule of procedures that were undertaken in this study are outlined in Table 3.

TABLE 3. Schedule of Study Procedures

Evaluation	Day of Evaluation									
	-7	0	1	2	3	7	14	21	28	90
Inclusion/Exclusion Criteria	X									
Informed Consent	X									
Medical and Skin Disease History	X									
Skin Type	X									
Physical Exam	X									X
Ophthalmic Examination	X									X
Assessment of Plaque Severity	X	X ^a	X	X	X	X	X	X	X	X
Assessment of Test Site Reactions		X ^{b,c}	X	X	X	X	X	X	X	X
Laboratory Tests	X		X		X	X			X	
Serum Pregnancy Tests	X									
Skin Sites Photographed		X ^c	X	X	X	X	X	X	X	X
LED and Laser Pre-verteporfin Light Dose (CS1, CS1D, CS1L)		X ^c								
Fluoroprobe Measurements		X	X	X	X					
Light Treatment (TS1-8, CS3)		X								
Assess Adverse Clinical Events		X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X

^a Up to 24 hours before drug infusion

^b CS1 only

^c Immediately before drug infusion

5.4.1 Pretreatment Procedures

Screening took place in the week before verteporfin infusion. At the screening visit (Day -7), the patients read and signed an Informed Consent and underwent a complete physical examination. The patient's name, age, sex, race, body weight (kg), and height (cm) were recorded. A detailed medical and psoriasis history was also taken. Patients underwent a complete ophthalmic examination which included measurement of visual acuity, slit-lamp examination, color vision assessment, dilated fundus examination, intraocular pressure tests, and visual field measurement.

A blood sample was collected for the laboratory tests described in Table 4.

TABLE 4. Clinical Laboratory Tests

Hematology	Urinalysis	Serum Chemistry	
- Hematocrit	- Appearance	- Albumin	- ALT
- Hemoglobin	- Bacteria	- BUN	- Alkaline phosphatase
- Platelets	- Bilirubin	- Bilirubin	- AST
- Reticulocytes	- Color	- Calcium	- GGT
- Total and differential leukocyte count	- Glucose	- Chloride	- LDH
- RBC	- Hemoglobin	- CO ₂ /HCO ₃	- Haptoglobin
- WBC	- Ketones	- Creatinine	- Triglycerides
	- pH	- Direct bilirubin	- Cholesterol
	- Protein	- Glucose	- HDL cholesterol
	- Specific gravity	- Potassium	- LDL cholesterol
	- Squamous epithelium	- Phosphorus	
	- Urine WBC	- Sodium	
	- Urobilinogen	- Total protein	
		- Uric acid	

A serum pregnancy test was also performed, where applicable.

Skin type was assessed at screening according to the criteria shown in Table 5.

TABLE 5. Skin Type Classification

Skin Type	Description
I	Always burns easily; never tans (sensitive)
II	Always burns easily; tans minimally (sensitive)
III	Burns moderately; tans gradually (light brown) (normal)
IV	Burns minimally; always tans well (moderate brown) (normal)
V	Rarely burns; tans profusely (dark brown) (insensitive)
VI	Never burns; deeply pigmented (insensitive)

Up to 24 hours before drug infusion, the Investigator selected areas of psoriasis plaque and normal skin from each patient and divide them into test sites as described in Section 5.3.1.2(a). The psoriasis sites were to have a minimum total score of 8.0 for erythema, scale, and elevation scores according to the lesion scoring system described in Section 5.5.1.2.

5.4.2 Treatment Day Procedures

Before the drug was infused, baseline plaque severity and test site reactions were assessed as described in Sections 5.5.1.2 and 5.5.3.6 below. The amount of verteporfin accumulating in the skin was measured using a fluorescent probe (i.e. "Fluoroprobe") as described in Section 5.5.2. Treatment sites were photographed and the control sites (CS1, CS1D, CS1L)

were then exposed to laser (Part A and B) or LED (Part B) light before drug infusion. The drug was then infused and three hours after infusion, the remaining treatment sites were exposed to light as described in Section 5.3.1.2 (a) and the Fluoroprobe measurements were repeated. Vital signs were monitored throughout the entire 45-minute infusion. According to an amendment dated 19 July 1994, patients enrolled in the Canadian center were also to have an ECG monitored during infusion. Adverse events were assessed in an ongoing fashion during the infusion procedure.

5.4.3 Follow-up Procedures

Samples for laboratory tests were collected on Days 1, 3, 7, and 28.

Test site reactions and psoriasis severity were assessed on Days 1, 2, 3, 7, 14, 21, 28, and 90. At 3 months, an eye examination (excluding the dilated fundus and slit lamp components) and a physical examination were performed. Concomitant medications and adverse events were documented at each visit. The Fluoroprobe measurements were to be performed (described in Section 5.5.2) on Days 1, 2, and 3 after drug infusion. Test site photographs were to be taken on Day 0 and on Days 1, 2, 3, 7, 14, 28, and 90.

5.5 Efficacy and Safety Variables

5.5.1 Efficacy Variables and Assessments

The primary efficacy variable was the change in plaque severity from baseline.

The severity of psoriasis at each lesion site was assessed using the 15-point scale shown in Table 6.

TABLE 6. Scoring System for the Severity of Psoriasis Plaques

Characteristic	Score	Description
Scaling	0	None
	1	Minimal: poorly defined scales
	2	Moderate: defined scales
	3	Severe: well-defined, raised scales with silvery appearance
	4	Extreme: scales cover plaque completely
Erythema	0	None
	1	Very mild: pink, barely perceptible
	2	Moderate: pale red, defined edges
	3	Strong: very red, area well-defined
	4	Extreme: dark red to slight eschar formation
Elevation	0	None
	1	Barely perceptible elevation
	2	Moderate elevation
	3	High elevation
	4	Extremely elevated; high ridge

This assessment was to be performed immediately before drug infusion (Day 0) and on Days 1, 2, 3, 7, 14, 21, 28, and 90 after verteporfin infusion.

The individual characteristics of scaling, erythema, and elevation were added together to yield an overall sum score (out of 15) for plaque severity. As described in inclusion criterion #2, the psoriasis plaque sites were to have a minimum severity sum score of 8.0. This assessment assumed that multiple treatment sites were independent of each other due to the limited area of light application. The percentage change from baseline in the plaque severity sum score was calculated for each site as follows:

$$\text{Percentage Change} = \frac{\text{Baseline sum score}^a - \text{Observed sum score}}{\text{Baseline sum score}} \times 100\%$$

^a Baseline sum score is the score measured immediately before drug infusion

According to this formula, a decrease in plaque severity would be represented by a positive number. An increase in plaque severity would be represented by a negative number.

Since the normal skin sites would have baseline scores of 0, they would not qualify for this assessment.

The three efficacy parameters described in the protocol were:

a) **Lesion Response to PDT**

A response was defined in the protocol as a $\geq 25\%$ decrease in plaque severity sum score at any test site compared to baseline (i.e. immediately before drug infusion) at any evaluation.

b) **Time to Lesion Response**

This parameter was originally defined as "Time taken for a lesion to clear". In the amendment dated April 11, 1994, it was changed to "Time to achieve evidence of a positive response" and redefined as the number of days from baseline (i.e. immediately before drug infusion) to the first evaluation with a decrease in the plaque severity sum score of $\geq 25\%$.

c) **Time to Lesion Recurrence**

This parameter was originally defined as "Duration of psoriatic clearing". In the amendment dated April 11, 1994, it was changed to "Time to recurrence", where any increase in the total score after a stable period of a positive response was to have been considered a recurrence. The protocol did not specify either the magnitude of the increase in the plaque severity score that qualified as a recurrence or the length of the stable period that was to precede it. The statistical analysis defined those parameters as described in Section 5.7.2.2.

5.5.2 Measurement of Verteporfin Accumulation in Skin

The amount of verteporfin accumulating in the skin was to be quantified at each time point after infusion by determining fluorescence in skin using a fluorescent probe (i.e. "Fluoroprobe") (5). Because of technical difficulties, the quantification of verteporfin using the Fluoroprobe was not completed and the results were not interpretable. The data collected are presented in Appendix E.4.

5.5.3 Safety Variables and Assessments

Safety was to be assessed through reporting of adverse events and examining changes from baseline in laboratory tests, vital signs, ophthalmic examinations, and test site reactions to PDT.

5.5.3.2 Adverse Events

Adverse Event Definitions and Reporting: Appendix E.3.4

The criteria for defining and reporting adverse events were as described in the protocol. Adverse events were monitored throughout the study in an ongoing fashion. The relationship of an adverse event to treatment was categorized as being definite, probable, possible, not probable, and unrelated. Adverse events that were definitely, probably, and possibly related to treatment were considered associated with treatment. Serious adverse events were those that were considered life-threatening, that required or prolonged hospitalization, that resulted from an overdose, or constituted a malignancy or congenital anomaly, or resulted in a permanent disability. Any serious adverse events were to be reported to the sponsor immediately.

5.5.3.3 Laboratory Data

Clinical laboratory tests for routine hematology, urinalysis, and blood chemistry were to be performed at the screening visit and on Days 1, 3, 7, and 28 after verteporfin infusion. Clinically significant laboratory values were to be reported to the Sponsor. Abnormal laboratory tests were to be repeated to confirm the findings.

5.5.3.4 Vital Signs

All patients were to have their vital signs (blood pressure, respiration, and heart rate) monitored at Time 0 and at 5 and 10 minutes after the start of the infusion and every 10 minutes thereafter until the end of the infusion. Vital signs were also to be monitored every hour after treatment until they returned to normal. Subsequent to an amendment dated April 11, 1994, an ECG was to be monitored during infusion in patients who were enrolled in the Canadian center.

5.5.3.5 Ophthalmic Examinations

A full ophthalmic examination was performed at screening. A partial examination that omitted the dilated fundus and slit-lamp procedures was repeated on Day 90 after verteporfin infusion.

5.5.3.6 Test Site Reactions to PDT

Erythema or edema at the test sites are expected skin reactions to PDT. An overdose of either drug or light could result in ulceration and necrosis of the skin. To optimize drug and light doses [see Section 5.3.1.4], skin reactions at the test sites were categorized according to the scoring system described in Table 7.

TABLE 7. Scoring System for Test Site Reactions

Severity Grade	Description		
0	No change		
1	Scattered macular or papular eruptions	OR	Erythema that is asymptomatic and minimally perceptible.
2	Scattered macular or papular eruption	OR	Erythema with pruritus or other associated symptoms or palpable edema.
3	Vesicular eruption	OR	Severe erythema or palpable edema extending beyond the area of exposure.
4	Skin ulceration other than superficial ulceration resulting from evolution of a vesicle ^a .		

^a A circumscribed, elevated, fluid-filled blister, 5 mm or less in diameter.

As described in the protocol, this assessment was to be performed immediately before drug infusion (Day 0) and on Days 1, 2, 3, 7, 14, 21, 28, and 90 after verteporfin infusion.

5.6 Data Quality Assurance

Inter-laboratory Standardization Methods: Appendix D.6

Infusion and light administration procedures were documented for each patient in their Case Report Form. Laser power output was monitored with a power meter and monochromator. The power meter and monochromator were calibrated annually to ensure accurate data measurements and the date of calibration was recorded on the CRF. The radiometer used to measure LED power density was calibrated semiannually and the date of calibration was recorded in the CRF.

The Clinical Study Monitor visited the study sites to ensure adherence to the protocol, proper completion of Case Report Form (CRFs), and maintenance of adequate source documentation. The CRFs were completed by the person administering the treatments and then reviewed and signed by the Investigator.

Laboratory tests were performed at an accredited laboratory at each center.

5.7 Statistical Methods

The analysis described in the protocol is summarized in this section. Changes to the analytical plan adopted for this report are described in Section 5.8.2.2.

5.7.1 Sample Size

No formal sample size calculations were specified in the original protocol. A minimum of 12 patients were to be enrolled in 2 centers. In the amendment dated July 19, 1994, the number of patients in Part A (laser treatments) was increased to 24. In Part B laser and LED treatments were used and the sample size was increased by 12 patients. The Sponsor felt that these enrollments would be adequate to assess safety and allow preliminary evaluation of drug and light dosing to be made.

5.7.2 Statistical Analysis Plan

5.7.2.1 Demographic Information

Patient demographic and background information were obtained at the screening interview. Continuous variables were summarized by mean, standard deviation, and ranges. Categorical variables were summarized by counts and percentages. The demographic information was tabulated by patient.

5.7.2.2 Efficacy Analysis

The efficacy objectives of the study were to estimate a) the lesion response rate to PDT, b) the time to lesion response and time to recurrence.

a) Lesion Response to PDT

As stated in the protocol, each lesion was treated as an individual experimental unit. A baseline measurement was made immediately before drug infusion (Day 0). The percent change in plaque severity from baseline for each test site at each evaluation was calculated as described in 5.5.1 and the results were tabulated. The lesion response rates at each evaluation were then tabulated. A comparison was made between laser and LED light for plaque response.

b) Time To Lesion Response And Recurrence

The following general considerations applied to both of the 2 time-to-event variables. If the patient was lost to follow-up, then that observation was to be considered censored at the time of last follow-up. The median number of days to a response and to a recurrence were estimated using the product limit survival method.

Time to lesion response was defined as the time from treatment (Day 0) to the first plaque evaluation showing a response (i.e. $\geq 25\%$ decrease in plaque severity sum

score from baseline). The median number of days to a first lesion response was calculated for each drug and light dose combination.

The report defined a recurrence as an increase in plaque severity sum score of ≥ 12.5 % following a stable period, defined as ≥ 1 week. Time to recurrence was defined as the time from the first evaluation showing a response to the next subsequent evaluation showing a recurrence.

5.7.2.3 Safety Analyses

Adverse Events were coded by body system using the Coding Symbols for Thesaurus of Adverse Reactions Terms (COSTART) dictionary. The findings were tabulated by COSTART body system category, severity and association with treatment. Associated Adverse Events are described in the report. Laboratory data were compiled and the results were tabulated. Vital signs were tabulated by patient.

5.8 Study Modifications

5.8.1 Protocol Amendments

Amendments: Appendix D.1.2

The original protocol was dated December 7, 1992. The 3 protocol amendments and their dates are summarized in Table 8.

TABLE 8. Protocol Amendments and Patients Affected

Protocol Amendment	Date of Amendment	Subject of Amendment	Number of Patients Enrolled^a
1	May 17, 1993	<ul style="list-style-type: none"> • Fourth skin site added 	7
2	April 11, 1994	<ul style="list-style-type: none"> • LED light treatment schedule added in Part B • Third study center added • The definition of significant phototoxicity was changed from Grade 3 to Grade 4 	18
3	July 19, 1994	<ul style="list-style-type: none"> • Patients with thrombophlebitis excluded • Females on long-term birth control included • ECG monitored during infusion • Sample size increased to 36 • Safety criteria changed 	19

^a Number of patients already enrolled at the time of the amendment.

In the amendment issued on May 17, 1993, a fourth test site up to 5 cm in diameter (TS4) was added to the treatment schedule.

In the amendment issued on April 11, 1994, a new treatment schedule including LED light was added and the treatment schedule was separated into Part A and Part B. A third study center and a new Investigator (Dr. Hruza, St. Louis) were added.

In the amendment issued on July 19, 1994, the following changes were instituted:

- The dose of verteporfin was to be reduced from 0.20 mg/kg to 0.15 mg/kg in the event of Grade 3 or higher skin toxicity at any treatment site.
- The number of patients who were to be treated with 0.20 mg/kg of verteporfin and light doses of 30, 45, and 60 J/cm² in Part B was changed from a minimum of 12 to a maximum of 12 patients. If there was no response or toxicity, the light dose was to be increased to 75 J/cm². If two patients developed a Grade-4 skin reaction at any site, the light dose was to be reduced by 15 J/cm². If a Grade 3 or higher skin reaction was observed at any treatment site at a verteporfin dose of 0.20 mg/kg, the data was to be reviewed and a decision was to be made whether to lower the drug or the light dose.

- The number of patients in Part A was changed from a minimum of 12 to a maximum of 24. In Part B the number of patients was changed from a minimum of 12 to a maximum of 12.
- The inclusion criteria were amended to include female patients who were on long-term birth control that would be readily maintained during the study.
- The exclusion criteria were amended to exclude patients with active thrombophlebitis. This amendment was requested by the Health Protection Branch of Health Canada and applied only to the Canadian center.
- Continuous cardiac monitoring consisting of vital signs and an ECG were required throughout the infusion period. Temperature recording was no longer required. This amendment was requested by the Health Protection Branch of Health Canada and applied only to the Canadian center.

As only 2 patients were enrolled under this amendment, these changes did not substantially affect the overall results of the study.

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

The protocol specified an enrollment target of 36 patients. The protocol stated that Part B of the study was to replace Part A and 12 patients were to have been enrolled in Part B. The study was terminated however, after only 3 patients had been enrolled in Part B because the Sponsor believed that the information collected was adequate to demonstrate the effectiveness of the LED source in activating verteporfin.

The protocol indicated that a baseline evaluation of plaque severity was to be performed on Day 0, "up to 24 hours before drug infusion". The correct nomenclature for this evaluation is in fact, Day-1 (i.e. before treatment) and this was the study day indicated on the CRF.

An additional assessment of plaque severity and test site reactions were performed on Day 60 in patients 7 and 13-21. The Day 0 test site reaction at CS1 was not assessed in patients 6, 16 and 18. Patient 20 had two CS2 sites assigned by the Investigator.

As mentioned in Section 5.5.2, the Fluoroprobe measurements were not performed in all patients or at all of the time points specified in the protocol. In many cases, the calibration step was omitted, resulting in an incomplete data set which was not interpretable. The method could not be validated and a decision was made not to analyze the data. The data are listed in Appendix E.4.

5.8.2.2 Changes in Data Analysis

As only 3 patients were enrolled in Part B, the patients in Part A and B were analyzed as a single study. Although the protocol mentioned patient response, the response rate of patients was not calculated as the same patient could have received different light doses at different lesions. The report used a more precise definition of recurrence and time to recurrence (see Section 5.7) as these were not detailed in the protocol. The percent change from baseline in plaque severity was calculated using the Day-7 evaluation as the baseline rather than the Day-1 as indicated in the protocol.

6. STUDY PATIENTS: DISPOSITION AND DEMOGRAPHY

6.1 Disposition of Patients

Lesion Response: Appendix A.3.1
Percent Change of Psoriasis Evaluation (SUM) from Baseline: Appendix E.2.2
Dose of Verteporfin Administered to Study Patients: Appendix E.3.1
Extent of Light Exposure for Treatment and Control Sites: Appendix E.3.2
Test Site Reactions to PDT: Appendix E.3.5

The disposition of study patients is summarized in Table 9.

TABLE 9. Disposition of Study Patients

Status	Number of Patients
Enrolled	21
Completing Part A	18
Completing Part B	3
Completing follow-up	21
Withdrawn	0

A total of 21 patients were enrolled in the study. Eighteen patients were treated according to the schedule described in the original protocol and the first amendment and 3 patients were treated according to Part B. All 21 patients completed the study to the final follow-up assessment and none were withdrawn.

The number of lesions treated at each drug and light dose is presented in Table 10.

TABLE 10. Number of Lesions Treated at each Drug and Light Dose

Drug Dose (mg/kg)	Light Dose (J/cm ²)	Number of Lesions	
		Laser	LED
CONTROL SITES			
0.15	0	6	0
	75 ^a	6	0
0.20	0	16	0
	60 ^a	3	3
	75 ^a	12	0
Subtotal		43	3
TREATMENT SITES			
0.15	25	8	0
	50	9	0
	75	7	0
0.20	25	14	0
	30	3	3
	45	3	3
	50	12	0
	60	3	3
	75	12	0
Subtotal		71	9
TOTAL		114	12

^a Light administered before drug infusion

Fifteen patients received a dose of 0.20 mg/kg and 6 received 0.15 mg/kg of verteporfin. Eighteen patients were treated with laser light only and 3 patients received both laser and LED light.

6.2 Data Sets Analyzed

All enrolled patients were included in the efficacy and safety analyses.

6.3 Demographic and Other Baseline Characteristics

Demographic and Baseline Data Summary Tables: Appendix A.1
Demographic and Baseline Data Listings: Appendix E.1

6.3.1 Demographic and Baseline Data for All Patients

The patient's demographics and baseline characteristics are summarized in Table 11.

TABLE 11. Summary of Baseline Demographic Characteristics

Variable	Number (%) of Patients n=21
GENDER	
Male	18 (86)
Female	3 (14)
SKIN TYPE	
II	7 (33)
III	14 (67)
AGE (years)	
Mean±SD	50±16
(Range)	(23-71)
HEIGHT (cm)	
Mean±SD	173.6±9.1
(Range)	(157.5-195.0)
WEIGHT (kg)	
Mean±SD	86.0±14.9
(Range)	(51.5-110.0)
PSORIASIS AGE AT ONSET	
Mean±SD	27.3±14.0
(Range)	(4-54)

Three women and 18 men were enrolled in this study. The patients were of Skin Types 2 and 3 and their ages ranged from 23-71 years.

6.3.2 Prior Medical and Psoriasis History

A variety of pre-existing medical conditions were present in the patients at the screening visit. These were generally chronic in nature and included asthma, hypertension, heart disease, essential tremor, and hypothyroidism.

The study patients used a variety of prior psoriasis medications and these are presented in Appendix E.1.2. All patients met the inclusion criteria and complied with the study directions

concerning concomitant and prior medication. The average age at the onset of psoriasis symptoms in the 21 patients was 27.3 years.

7. PROTOCOL DEVIATIONS

Extent of Light Exposure for Treatment and Control Sites: Appendix E.3.2

No patients were excluded from the analysis as a result of protocol deviations.

8. EFFICACY RESULTS

8.1 Efficacy Results

Lesion Response: Appendix A.3.1
Percent Change of Psoriasis Severity (Sum) from Baseline: Appendix E.2.2
Extent of Light Exposure for Treatment and Control Sites: Appendix E.3.2

8.1.1 Lesion Response to PDT

The responses of all treatment and control sites are summarized by drug and light dose and by day of assessment in Appendix A.3.1. The percent change in psoriasis severity from baseline is also listed individually for all patients in Appendix E.2.2.

The lesion response rates to PDT after laser light for all patients are presented in Table 12.

TABLE 12. Lesion Response for all Patients after Laser Light (Part A and B)

Drug Dose (mg/kg)	Light Dose (J/cm²)	Number of Lesions Evaluated	Number (%) of Lesions Responding
CONTROL SITES			
0.15	0	6	3 (50)
	75 ^a	6	4 (67)
0.20	0	16	8 (50)
	60 ^a	3	2 (67)
	75 ^a	12	5 (42)
Control site subtotal		43	22 (51)
TREATMENT SITES			
0.15	25	8	5 (63)
	50	9	4 (44)
	75	7	5 (71)
0.20	25	14	4 (29)
	30	3	3 (100)
	45	3	3 (100)
	50	12	9 (75)
	60	3	3 (100)
	75	12	12 (100)
Treatment site subtotal		71	48 (68)
Total for all sites		114	70 (61)

^a Light administered before drug infusion.

As described in Section 5.5.1, the normal skin sites had plaque severity scores of zero and did not qualify for the analysis of response rates. Of the 71 treatment sites that received PDT (i.e. both drug and light), 48 (68%) responded at one or more of the follow-up visits. The response rate at the 0.20 mg/kg drug dose (72%; 34/47 sites) was higher than the response rate at the 0.15 mg/kg drug dose (58%; 14/24 sites). The overall response rate among the control sites (plaques that received only drug or light but not both) was 51% (22/43 sites).

A comparison of the lesion responses in the 3 patients who received both laser and LED light in Part B is presented in Table 13.

TABLE 13. Lesion Response to PDT: LED Versus Laser Light

Drug Dose (mg/kg)	Light Dose (J/cm ²)	LED			Laser		
		Site	Number of Lesions Evaluated	Number (%) of Lesions Responding	Site	Number of Lesions Evaluated	Number (%) of Lesions Responding
CONTROL SITES							
0.20	60 ^a	CS1D	3	3 (100)	CS1L	3	2 (67)
Subtotal			3	3 (100)		3	2 (67)
TREATMENT SITES							
0.20	30	DS1	3	3 (100)	LS1	3	3 (100)
	45	DS2	3	3 (100)	LS2	3	3 (100)
	60	DS3	3	2 (67)	LS3	3	3 (100)
Subtotal			9	8 (89)		9	9 (100)

^a Light administered before drug infusion.

Although only 3 patients were treated according to Part B of the schedule, the laser and LED light sources appear to evoke a similar response rate in these patients.

8.1.2 Time To Lesion Response and Recurrence

Statistical Output: Appendix B

Results for all test sites are presented in Table 14.

TABLE 14. Time to Lesion Response and Time to Recurrence

Drug Dose (mg/kg)	Light Dose (J/cm²)	Number(%) of Lesions Responding^a		Median Number of Days to Response	Number (%) of Lesions Recurring		Median Number of Days to Recurrence
CONTROL SITES							
0.15	0	3	(50)	92	1	(33)	— c
	75 ^b	4	(67)	61	1	(25)	— c
0.20	0	8	(50)	91	4	(50)	59
	60 ^b	2	(67)	58	2	(100)	31
	75 ^b	5	(42)	91	1	(20)	— c
Subtotal		22	(51)	91	9	(41)	82
TREATMENT SITES							
0.15	25	5	(63)	30	4	(80)	77
	50	4	(44)	— c	4	(100)	39
	75	5	(71)	22	4	(80)	47
0.20	25	4	(29)	— c	1	(25)	— c
	30	3	(100)	21	2	(67)	36
	45	3	(100)	54	2	(67)	44
	50	9	(75)	13	5	(56)	62
	60	3	(100)	14	2	(67)	29
75	12	(100)	11	7	(58)	27	
Subtotal		48	(68)	21	31	(65)	50
TOTAL		70	(61)		40	(57)	

^a From Table 12.

^b Light administered before drug infusion.

^c Survival analysis unable to estimate a median value.

The results showed that the PDT treatment sites tended to respond earlier than the control sites (e.g. 21 days versus 91 days). The recurrence rate among the treatment sites was 65% – i.e. more than half of the sites had a recurrence within the 12 week study period. The median time to recurrence at these treatment sites was 50 days.

The control sites had a relatively high response rate (51%) and a recurrence rate of 41%. The median number of days to a recurrence was 82.

8.1.3 Discussion of Efficacy Results

Overall, 68% of the treatment sites responded after one course of verteporfin PDT. The response rate among the control sites was 51%. The relatively high response rate among the control sites is probably related to the lenient definition of a response used in this study and the fluctuating nature of the disease. It is also possible that some of the control plaques may not have been adequately covered and may have inadvertently been exposed to ambient light following PDT.

The median time to a response was 21 days for the treatment sites and 91 days for the control sites. Of the 48 responding treatment lesions, 31 (65%) recurred with a median time to recurrence of 50 days. The other 17 responding lesions (35%) were still in response at the last follow-up visit at 12 weeks. The median time to a response of the treatment sites (21 days) was much shorter than that of the control sites (91 days) as was the time to recurrence (50 days vs 82 days).

In general, the highest response rates were observed in the patients who received 0.20 mg/kg of verteporfin. The response rates in lesions exposed to laser and LED light were similar, suggesting that the LED light with an emission spectrum of 688 ± 10 nm can be used to activate verteporfin. The recurrence rate among responding lesions was very high (65%) but this is not unexpected after a single treatment course in a disease where multiple treatments are usually required to sustain a response.

9. SAFETY RESULTS

9.1 Extent of Exposure

*Dose of Verteporfin Received by each Patient in Relation to: Appendix A.2.2
Body Weight and Surface Area*

Demographics: Appendix E.1.3

Dose of Verteporfin Administered to Study Patients: Appendix E.3.1

Extent of Light Exposure for Treatment and Control Sites: Appendix E.3.2

9.1.1 Exposure to Trial Treatments

The dose of verteporfin received by each patient is presented in Table 15.

TABLE 15. Dose of Verteporfin Received by Each Patient

Patient Number	Weight (kg)	Verteporfin Dose (mg/kg)	Total Drug Dose ^a (mg)	Total Drug Dose/BSA (mg/m ²)
1	87.3	0.20	17.50	8.5
2	85.0	0.20	17.00	9.1
3	69.1	0.20	13.80	7.3
4	92.3	0.20	18.50	9.1
5	89.0	0.20	17.80	8.4
6	73.5	0.20	14.70	7.8
7	80.0	0.20	16.00	8.6
8	78.2	0.20	15.60	8.0
9	97.3	0.20	19.50	9.9
10	110.0	0.20	22.00	9.9
11	86.7	0.20	17.30	8.4
12	90.0	0.20	18.20	8.8
13	84.0	0.15	12.60	6.2
14	93.0	0.15	13.90	6.6
15	100.0	0.15	15.00	7.2
16	109.0	0.15	16.40	6.8
17	65.0	0.15	9.80	5.6
18	98.5	0.15	14.50	6.7
19	102.3	0.20	20.50	9.6
20	67.3	0.20	13.50	7.5
21	51.5	0.20	10.30	6.7
			MEAN	7.9

^a weight x verteporfin dose = total drug dose

All patients received a dose of either 0.15 mg/kg (6 patients) or 0.20 mg/kg of verteporfin (15 patients) according to the protocol.

The dose of verteporfin received by each patient is expressed in relation to body weight and surface area in Appendix E.3.1.1. The total verteporfin dose ranged from 9.80 to 22.00 mg/patient. When expressed in terms of body surface area, the dose of verteporfin ranged from 5.6 mg/m²-9.9 mg/m². The mean drug dose was 7.9 mg/m².

The light doses applied and light sources used are presented in Section 6.1 (Table 10) above.

9.1.2 Exposure to Concomitant Treatment

Concomitant Medications: Appendix E.3.3

The study patients had used a variety of psoriasis treatments before enrollment. All of the patients complied with the prohibition against concurrent psoriasis therapy during the study. A variety of medications were used to treat pain and headache, other pre-existing medical conditions and psoriasis symptoms at non-treatment sites. The most commonly used medication was acetaminophen (Tylenol, Tylenol 3) which was used by 13 patients. These medications were judged not to have affected the study assessments or response of the treatment sites to the study treatment.

9.2 Overview of Adverse Events

An overview of adverse event categories is presented in Table 16.

TABLE 16. Overview of Adverse Event Categories

Adverse Event Category	Number of Patients n=21	
	Number of Patients with Any Adverse Event	Number of Patients with an Associated Adverse Event^a
Patients with any adverse event	19	18
Withdrawal due to an adverse event	0	0
Other serious adverse events ^b	3	2
Deaths	0	0

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

^b Serious adverse events not leading to death or withdrawal.

Adverse events were observed in 19 patients. These events were classified as being associated with treatment in 18. No deaths, or withdrawals due to adverse events were observed during this study.

9.2.1 All Adverse Events

Adverse Event Listing: Appendix E.3.4.1
COSTART Terms: Appendix E.3.4.2

Adverse events are presented by COSTART body system and severity in Table 17.

TABLE 17. Summary of All Adverse Events

(Page 1 of 2)

BODY SYSTEM/ COSTART Adverse Events	Number (%) of Patients n=21	Number of Events	Grade of Severity (Number of Events)		
			Mild	Moderate	Severe
PATIENTS WITH AT LEAST 1 AE	19 (90)				
BODY AS A WHOLE	13 (62)	35			
Abdominal pain	2 (10)	2	1	1	0
Accidental injury	2 (10)	3	3	0	0
Asthenia	3 (14)	3	3	0	0
Back pain	1 (5)	1	1	0	0
Chest pain	1 (5)	1	1	0	0
Chills	2 (10)	3	3	0	0
Fever	1 (5)	1	1	0	0
Headache	9 (43)	14	12	2	0
Infection	1 (5)	1	1	0	0
Pain	4 (19)	4	2	2	0
Photosensitivity	2 (10)	2	2	0	0
CARDIOVASCULAR	1 (5)	2			
Spider angioma	1 (5)	1	1	0	0
Vasodilatation	1 (5)	1	1	0	0
DIGESTIVE	4 (19)	9			
Constipation	1 (5)	1	1	0	0
Diarrhea	2 (10)	2	2	0	0
Flatulence	1 (5)	1	0	1	0
Melena	1 (5)	1	1	0	0
Nausea	2 (10)	2	0	2	0
Rectal bleeding	1 (5)	1	1	0	0
Vomiting	1 (5)	1	0	1	0
HEMIC AND LYMPHATIC	2 (10)				
Ecchymosis	2 (10)	2	2	0	0
MUSCULOSKELETAL	3 (14)	3			
Arthralgia	1 (5)	1	1	0	0
Myalgia	1 (5)	1	1	0	0
Tendonitis	1 (5)	1	1	0	0
NERVOUS SYSTEM	3 (14)	4			
Dizziness	1 (5)	1	1	0	0
Emotion lability	1 (5)	1	0	0	1
Hypotonia	1 (5)	1	1	0	0
Insomnia	1 (5)	1	1	0	0
RESPIRATORY SYSTEM	6 (29)	12			
Cough	2 (10)	2	1	1	0
Dyspnea	1 (5)	1	1	0	0
Pharyngitis	4 (19)	4	3	1	0
Rhinitis	3 (14)	4	4	0	0
Sinusitis	1 (5)	1	1	0	0
SKIN AND APPENDAGES: DERMATOSES	7 (33)	11			
Blisters	1 (5)	1	0	1	0
Dry skin	2 (10)	2	2	0	0
Infection	1 (5)	1	0	1	0
Pruritus	1 (5)	1	1	0	0
Psoriatic pruritus	1 (5)	2	1	0	1
Rash	1 (5)	1	1	0	0
Skin hypertrophy	1 (5)	1	1	0	0
Skin benign neoplasia	1 (5)	1	1	0	0
Skin nodule	1 (5)	1	1	0	0
SKIN AND APPENDAGES: GENERAL	1 (5)	2			
Psoriasis worsened	1 (5)	1	1	0	0
Psoriatic pruritus	1 (5)	1	1	0	0

TABLE 17. Summary of All Adverse Events

(Page 2 of 2)

BODY SYSTEM/ COSTART Adverse Events	Number (%)		Number of Events	Grade of Severity (Number of Events)		
	of Patients n=21			Mild	Moderate	Severe
SKIN AND APPENDAGES:						
TREATMENT SITES — BEFORE						
Warmth	1	(5)	1	1	0	0
SKIN AND APPENDAGES:						
TREATMENT SITES — DURING						
Burning	1	(5)	1	1	0	0
Discomfort	2	(10)	3	3	0	0
Pruritus	3	(14)	6	3	3	0
Warmth	5	(24)	11	9	1	1
SKIN AND APPENDAGES:						
TREATMENT SITES — AFTER						
Burning	1	(5)	1	0	1	0
Discomfort	3	(14)	5	4	1	0
Edema	6	(29)	6	3	3	0
Erythema	2	(10)	2	1	1	0
Koebner reaction	1	(5)	1	0	1	0
Local eschar	2	(10)	2	0	1	1
Pain	9	(43)	14	8	5	1
Pruritus	2	(10)	2	1	1	0
Purpura	2	(10)	2	1	1	0
Scab	1	(5)	1	1	0	0
Scar	1	(5)	1	0	0	1
Skin discolor	3	(14)	6	5	1	0
Skin necrosis	1	(5)	2	0	0	2
Skin ulcer	1	(5)	1	0	0	1
Sweat	1	(5)	1	1	0	0
Tenderness	7	(33)	8	6	1	1
Warmth	1	(5)	1	1	0	0
SPECIAL SENSES						
Eye hemorrhage	1	(5)	2	1	1	0
Eye irritation	1	(5)	1	1	0	0
Eye pain	1	(5)	1	1	0	0
Glare	4	(19)	4	3	1	0
Photophobia	1	(5)	1	1	0	0
Ear disorder ^a	1	(5)	1	0	1	0
Vision abnormal	2	(10)	2	1	1	0

^a described as a plugged ear

The most common systemic adverse event was headache (9 patients). The most common local adverse events were pain (9 patients), tenderness (7 patients), and edema (6 patients) at the treatment sites after light application. During light application, the most common adverse event was warmth (5 patients) at the treatment sites. In one patient, exacerbation of a pre-existing benign punctate facial angioma as a result of shaving was noted.

9.2.2 Associated Adverse Events

Associated adverse events were those considered to be definitely, probably, and possibly related to study therapy (definitely not and probably not were considered unrelated).

Adverse events associated with treatment are presented by COSTART body system and severity in Table 18.

TABLE 18. Summary of Associated^a Adverse Events

BODY SYSTEM/ COSTART Adverse Events	Number (%) of Patients n=21		Number of Events	Grade of Severity (Number of Events)		
				Mild	Moderate	Severe
PATIENTS WITH AT LEAST 1 AE	18	(88)				
BODY AS A WHOLE	7	(33)	11			
Asthenia	1	(5)	1	1	0	0
Chills	2	(10)	2	2	0	0
Headache	4	(19)	6	4	2	0
Photosensitivity	2	(10)	2	2	0	0
CARDIOVASCULAR	1	(5)	1			
Vasodilatation	1	(5)	1	1	0	0
DIGESTIVE	1	(5)	1			
Diarrhea	1	(5)	1	1	0	0
SKIN AND APPENDAGES:						
DERMATOSES	1	(5)	1			
Rash	1	(5)	1	1	0	0
SKIN AND APPENDAGES:						
TREATMENT SITES — BEFORE	1	(5)	1			
Warmth	1	(5)	1	1	0	0
SKIN AND APPENDAGES:						
TREATMENT SITES — DURING	7	(33)	21			
Burning	1	(5)	1	1	0	0
Discomfort	2	(10)	3	3	0	0
Pruritus	3	(14)	6	3	3	0
Warmth	5	(24)	11	9	1	1
SKIN AND APPENDAGES:						
TREATMENT SITES — AFTER	14	(67)	55			
Burning	1	(5)	1	0	1	0
Discomfort	3	(14)	5	4	1	0
Edema	6	(29)	6	3	3	0
Erythema	2	(10)	2	1	1	0
Koebner	1	(5)	1	0	1	0
Local eschar	2	(10)	2	0	1	1
Pain	9	(43)	13	7	5	1
Pruritus	2	(10)	2	1	1	0
Purpura	2	(10)	2	1	1	0
Scab	1	(5)	1	1	0	0
Scar	1	(5)	1	0	0	1
Skin discoloration	3	(14)	6	5	1	0
Skin necrosis	1	(5)	2	0	0	2
Skin ulcer	1	(5)	1	0	0	1
Sweating	1	(5)	1	1	0	0
Tenderness	7	(33)	8	6	1	1
Warmth	1	(5)	1	1	0	0
SPECIAL SENSES	6	(29)	9			
Eye irritation	1	(5)	1	1	0	0
Eye pain	1	(5)	1	1	0	0
Glare	4	(19)	4	3	1	0
Photophobia	1	(5)	1	1	0	0
Vision abnormal	2	(10)	2	1	1	0

^a Definitely, probably, and possibly are considered associated with treatment; definitely not, possibly not, and remotely are considered unrelated.

Most of the associated adverse events occurred at the treatment sites. During treatment, the most common event was warmth at the treatment sites (5 patients). Sensations of warmth are expected during light application and they were severe in 1 instance but mild-moderate in all others. After treatment, the more commonly reported adverse events were pain (9 patients), tenderness (7 patients), and edema (6 patients) at the treatment sites. In 2 cases the symptoms were severe. In most cases the symptoms lasted for less than 5-7 days and were easily controlled with analgesics.

The more common systemic adverse events that were considered to be associated with treatment were headache (4 patients), glare (4 patients), chills (2 patients), and photosensitivity (2 patients). The photosensitivity reactions were described by the Investigators as a "burnt feeling in the skin after approximately 30 minutes exposure to outdoor light" (patient #7) and a "sunburn-like sensation of the inner right forearm that was not accompanied by erythema" (patient #21). No further information on these events was available.

Nine adverse events affecting the eye were reported in 6 patients. These included glare (4 patients), eye irritation (1 patient), eye pain (1 patient), photophobia (1 patient), and vision abnormal (described by the Investigator as "blurry vision" for patient #4 and "a hazy film in front of the eyes" for patient #7). The screening fundoscopic examination in patient #4 revealed mild venous tortuosity in both eyes but no other abnormalities. The screening ophthalmic examination of patient #7 was normal. Glare was reported by 4 patients: in 3 cases it occurred after the patients had been exposed to bright light or had removed their protective sunglasses. The fourth patient retrospectively reported a mild transient sensitivity to light.

All of these events were mild-moderate in intensity. In most cases, the symptoms occurred within a week of treatment and they were of short duration. All symptoms had fully resolved by the end of the study (Day 90).

9.2.3 Special Safety Issues

9.2.3.1 Test Site Reactions to PDT

Demographics: Appendix E.1.3
Dose of Verteporfin Received by Each Patient in Relation to: Appendix E.3.1.1
Body Weight and Surface Area
Extent of Light Exposure for Treatment and Control Sites: Appendix E.3.2
Test Site Reactions to PDT: Appendix E.3.5

The test site reactions to PDT are presented by treatment and control site in Table 19 (laser sites only) and in Table 20 (laser and LED sites in Part B).

TABLE 19. Test Site Reactions to PDT (Laser Light Only) in Parts A and B

Drug Dose (mg/kg)	Laser Light Dose (J/cm ²)	Number of Sites	Highest Grade of Skin Reaction Number (%) of Treatment Sites							
			1	2	3	4				
NORMAL SKIN SITES										
0.15	75	6	3 (50)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.20	60	3	0 (0)	2 (67)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)
	75	12	2 (17)	8 (67)	1 (8)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal		21	5 (24)	13 (62)	1 (5)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)
CONTROL SITES										
0.15	0	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	75 ^a	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.20	0	16	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	60 ^a	3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	75 ^a	12	2 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal		43	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TREATMENT SITES										
0.15	25	8	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	50	9	4 (44)	1 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	75	7	2 (29)	3 (43)	2 (29)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.20	25	14	6 (43)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	30	3	1 (33)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	45	3	0 (0)	1 (33)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)
	50	12	3 (25)	6 (50)	3 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	60	3	0 (0)	1 (33)	1 (33)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)
	75	12	0 (0)	5 (42)	6 (50)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal:		71	16 (23)	18 (25)	13 (18)	3 (4)	0 (0)	0 (0)	0 (0)	0 (0)
TOTAL:		135	23 (17)	31 (23)	14 (10)	5 (4)	0 (0)	0 (0)	0 (0)	0 (0)

^a Light administered before drug infusion

No skin reactions were observed in the 22 control sites (CS2) that were not exposed to light.

In the control sites that were exposed to light before drug infusion (i.e. CS1, CS1L), Grade-1 skin reactions were observed in 2/21 (10%) sites and these occurred at the highest dose of light (75 J/cm²).

In the normal skin sites, PDT reactions ≥ Grade 3 were observed in 3/21 (14%) sites.

At the treatment sites, 16 skin reactions \geq Grade 3 were observed. These were more common at light doses ≥ 45 J/cm². Below 45 J/cm², only one Grade-3 reaction was observed. This was also somewhat dependent upon the verteporfin dose administered. For example, in patients who received 0.15 mg/kg of verteporfin, only 2 reactions \geq Grade 3 were observed out of 24 sites (8%) and these reactions only occurred at sites that received 75 J/cm² of light. In contrast, in patients who had received 0.20 mg/kg of verteporfin 14 reactions \geq Grade 3 were observed out of 47 sites (30%) that had received light doses of 30-75 J/cm².

All 5 of the Grade-4 skin reactions occurred in 2 patients (Patients 10 and 19). These 2 patients had high baseline weights, resulting in a high total dose of verteporfin as shown in Table 15 (i.e. 22.0 mg and 20.5 mg). When the drug dose was expressed in terms of body surface area, rather than weight, the dose of drug per square meter was higher in these two patients than it was in all but 1 of the other patients (see Table 15 and Appendix E.3.1.1). Only one other patient (Patient 9) received a comparable dose per BSA. This individual (Patient 9) however, was one of only two patients in this study in whom no adverse events were reported.

The highest grade of skin reactions of the 3 patients in Part B of the study who were treated with both LED and laser light are presented in Table 20.

**TABLE 20. Skin Reactions in Patients Receiving
0.20 mg/kg of Verteporfin (Part B)**

Patient Number	Test Site	LED		Laser		
		Light Dose (J/cm ²)	Skin Reaction Grade	Test Site	Light Dose (J/cm ²)	Skin Reaction Grade
NORMAL SKIN SITES						
19	CS3D	60	4	CS3L	60	4
20	CS3D	60	1	CS3L	60	2
21	CS3D	60	2	CS3L	60	2
CONTROL SITES						
19	CS1D	60	0	CS1L	60	0
20	CS1D	60	0	CS1L	60	0
21	CS1D	60	0	CS1L	60	0
TREATMENT SITES						
19	DS1	30	2	LS1	30	3
	DS2	45	3	LS2	45	4
	DS3	60	4	LS3	60	4
20	DS1	30	0	LS1	30	0
	DS2	45	0	LS2	45	0
	DS3	60	0	LS3	60	3
21	DS1	30	1	LS1	30	1
	DS2	45	2	LS2	45	2
	DS3	60	2	LS3	60	2

From the small amount of data available, laser light appears to be associated with slightly higher grades of skin reaction than LED light.

9.2.3.2 Ophthalmic Examinations

Ophthalmic Examinations: Appendix E.3.7

A subconjunctival hemorrhage was noted in the left (OS) eye of patient 13 at screening but this had resolved at the Day 90 follow-up examination. A subconjunctival hemorrhage was noted in the right (OD) eye of patient 16 at the Day 90 follow-up examination which was not present at screening.

The fundoscopic examination performed at screening revealed mild venous tortuosity in both eyes of patient 4. In patient 9, drusen formations were noted in both eyes and in patient 19 an asteroid hyalosis of the right (OD) eye was noted. No other ocular abnormalities were observed in the other study patients.

9.3 Deaths, Withdrawals, and Other Serious or Clinically Significant Adverse Events

Demographics: Appendix E.1.3

Dose of Verteporfin Administered to Study Patients: Appendix E.3.1

Serious Adverse Events: Appendix E.3.4.3

No deaths or withdrawals occurred during this study. Three patients reported 4 serious adverse events during this study. Two patients had 3 Grade-4 skin reactions that were considered treatment-associated serious adverse events by the Investigators. The three Grade-4 skin reactions are summarized in Table 21.

TABLE 21. Serious Adverse Events Associated with Treatment

Adverse Event Number ^a	Patient Number	Drug Dose (mg/kg)	Site Affected	Site Description	Light Source	Assigned Light Dose (J/cm ²)	Description
1	10	0.20	CS3	Normal skin	Laser	75	Grade 4 skin toxicity resulting in necrosis and Koebnerization
			TS3	Plaque	Laser	75	
2	19	0.20	LS2	Plaque	Laser	45	Grade-4 skin toxicity resulting in necrosis and scar formation
3	19	0.20	CS3D	Normal skin	LED	60	Grade-4 skin toxicity resulting in ulceration and Koebnerization
			CS3L	Normal skin	Laser	60	Grade-4 skin toxicity resulting in necrosis and scar formation
			DS3	Plaque	LED	60	Grade-4 skin toxicity resulting in necrosis and scar formation
			LS3	Plaque	Laser	60	Grade-4 skin toxicity resulting in necrosis and scar formation

^a Adverse events were counted separately by light dose.

The third patient (Patient #7), had a serious adverse event described by the Investigator as "severe marital stress" that was not related to treatment.

The Grade-4 skin reactions at the test sites occurred in 2 patients who had received 0.20 mg/kg of verteporfin and light doses ranging from 45-75 J/cm². Two of these adverse events occurred in Patient 19 at light doses of 45 and 60 J/cm². The third event occurred in Patient 10 at a dose of 75 J/cm². Of the 7 sites affected, 3 were normal skin control sites and 4 were plaque sites. Two of the 7 sites involved were LED sites and 5 of them were laser sites.

9.4 Laboratory Data

Out of Range Laboratory Values: Appendix A.2.1

No clinically significant abnormalities were observed during the study.

9.5 Vital Signs and Other Physical Findings

Vital Signs: Appendix E.3.6

Heart rate, blood pressure, and respiration rate remained normal before, during, and after drug infusion in all of the study patients.

9.6 Discussion of Safety Results

Verteporfin was well-tolerated by the patients in this study. No signs of clinically significant systemic toxicity or laboratory abnormality were observed in any patient. The most frequent adverse events that were considered to be treatment-associated were pain (9 patients), tenderness (7 patients), and edema (6 patients) at the treatment sites. These symptoms were predominantly of mild intensity and short duration. Grade-4 skin reactions were observed in 2 patients. The total amounts of verteporfin infused in these 2 patients were higher than in the other 19 patients due to the higher weight of these individuals. Since PDT for this indication relies on surface illumination to activate the drug, it may be more appropriate to base the dose of verteporfin in future studies on body surface area rather than weight.

The adverse events at the test sites are consistent with the pharmacological action of PDT. The symptoms were completely reversible and easily controlled with analgesic treatments.

The majority of skin reactions \geq Grade 3 were observed in treatment sites that received \geq 45 J/cm² of light following a verteporfin dose of 0.20 mg/kg. At the drug dose of 0.15 mg/kg, Grade 3 skin reactions only occurred at the 75 J/cm² light dose.

Local skin reactions were similar in patients who received the same light dose from either the laser source or the LED source.

10. DISCUSSION AND OVERALL CONCLUSIONS

- A single verteporfin treatment course had a modest treatment effect (i.e. a response rate of 68% at the treatment sites compared to 51% of the control sites).
- A relatively lenient definition ($\geq 25\%$ decrease in plaque severity score from baseline) was used to describe a response. This was reasonable for a Phase I study involving only a single treatment course as other current therapies for psoriasis required multiple treatments to achieve a response. It is unknown at this time whether the responses seen in the control sites were due to the fluctuating nature of the disease or the possibility that some control plaques may have inadvertently been exposed to ambient light following PDT. The highest response rate after PDT was in patients who had received 0.20 mg/kg of drug and ≥ 30 J/cm² of light. The recurrence rate among responding lesions was very high (65%).
- Most of the skin reactions \geq Grade 3 were observed in sites that received light doses ≥ 45 J/cm² and in patients who had received 0.20 mg/kg of verteporfin. The systemic safety profile of verteporfin is good. These were largely confined to the treatment sites and were mostly mild to moderate in severity, completely reversible, and easily controlled with analgesic treatment.
- In 3 patients who received both laser and LED light the lesion response rates and PDT-induced skin reactions were comparable, suggesting that the LED panels that emit light at 688 ± 10 nm can be used to activate verteporfin.
- Due to technical difficulties, it was not possible to determine the distribution of verteporfin in skin.
- Based on the results from this study, a verteporfin dose of 0.20 mg/kg and LED light exposures < 45 J/cm² (e.g. 30 J/cm²) appear to have the potential for inducing a response without provoking unacceptable skin reactions.
- Drug dose regimens based on body surface area might be more appropriate as they would avoid potential overdoses in obese patients.

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CLINICAL STUDY REPORT: BPD 002 AMENDMENT NO. 1 DATED 8 JULY 1999

DRUG NAME: VERTEPORFIN FOR INJECTION

**TITLE AND NAME: A PHASE I/II PHOTODYNAMIC THERAPY STUDY FOR THE
EVALUATION OF INTRAVENOUS BPD-MA IN THE
TREATMENT OF PSORIASIS DATED 21 MAY 1999**

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CLINICAL STUDY REPORT: BPD 002 AMENDMENT NO. 1 DATED 8 JULY 1999

DRUG NAME: VERTEPORFIN FOR INJECTION

TITLE AND NAME: A PHASE III PHOTODYNAMIC THERAPY STUDY FOR THE
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Reason for Revision: To correct the treatment dates for Patients 1 and 6.

Amendment: Appendix E.3.1, Dose of Verteporfin Administered to Study
Patients, is replaced.

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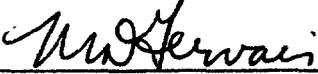
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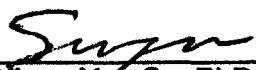
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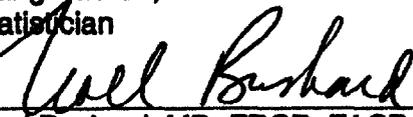
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Amendment: Page v, Table of Contents, is replaced.

Page 52, Section 12, Appendices, is replaced.

Page 133, Appendix C, Patient Capsule Summaries, is replaced (new title page + three capsule summaries, as pages 133, 133a, 133b, and 133c).