- Visits
  - Screen
    - Enrollment Form
    - Inclusion Criteria
    - Exclusion Criteria
    - Demography
    - Informed Consent
    - Psychiatric History
    - Medical and Surgical History
    - Psychotropic Drug Treatment History
    - Physical Exam
    - Vital Signs
    - Laboratory
    - 12-Lead ECG
    - Mini-Mental State Examination
    - Cornell Scale For Depression in Dementia
  - Baseline
    - Randomization
    - Vital Signs
    - Mini-Mental State Examination
    - Cornell Scale For Depression in Dementia
  - Week 2
    - Vital Signs
    - Laboratory
    - Cornell Scale for Depression in Dementia
    - Clinical Global Impression
  - Week 24
    - Physical Examination
    - Vital Signs
    - Laboratory
    - 12-Lead ECG
    - Mini-Mental State Examination
    - Cornell Scale For Drepression in Dementia
    - Clinical Global Impression
  - End of Study / Termination
    - Termination
  - Running Records
    - Study Medication Inventory
    - Medication Record
    - Adverse Events
    - Prior/Concomitant Medications
- Domains
  - 12-Lead ECG
    - Screen
    - Week 24
  - Adverse Events
    - Running Records
  - Clinical Global Impression
    - Week 2
    - Week 24

Cornell Scale for Depression in Dementia
- Screen
- Baseline
- Week 2
- Week 24

Demography
- Screen

Enrollment Form
- Screen

Inclusion Criteria
- Screen

Informed Consent
- Screen

Exclusion Criteria
- Screen

Laboratory
- Screen
- Week 2
- Week 24

Medication Records
- Running Records

Medical and Surgical History
- Screen

Mini-Mental State Examination
- Screen
- Baseline
- Week 24

Physical Examination
- Screen
- Week 24

Prior/Concomitant Medications
- Running Records

Psychiatric History
- Screen

Psychotropic Drug Treatment History
- Screen

Randomization
- Baseline

Study Medication Inventory
- Running records

Termination
- End of Study / Termination

Vital Signs
- Screen
- Baseline
- Week 2
- Week 24

DM=Demographics

CDISC Study CDISC01	

Enrollment Form

Enroll the subject by entering the 3-digit Site # and the 5-digit Subject ID#

Site #	__ __ __	***SITEID***

Subject ID#	__ __ __ __ __	***SUBJID***

SC=Subject Characteristics

Subject Initials	__ __ __	***SCORRES when SCTESTCD = SUBJINIT***

Form Design Note:
Subject ID is mapped forward to the Subject Demographic Data eCRF.

IE=Inclusion/Exclusion

CDISC Study	*VISIT* Screening
CDISC01	Assessment Date: _____ *IEDTC* _____

ELIGIBILITY CRITERIA

INCLUSION CRITERIA *IECAT* Check the appropriate response *IETEST*		**Yes**	**No**
1. Is age 18 - 85.	*IEORRES when IETESTCD = INCL01*	☐	☐
2. Has Xyz disease of at least 10 weeks duration confirmed by biopsy	*IEORRES when IETESTCD = INCL02*	☐	☐
3. Did not respond to a standard course of medication ABC.	*IEORRES when IETESTCD = INCL03*	☐	☐

*All **Inclusion Criteria** questions 1-3 must be answered **YES** to enter the study.*

IE=Inclusion/Exclusion

CDISC	VISIT Screening
Study CDISC01	IEDTC Assessment Date: _____/_____/_____

ELIGIBILITY CRITERIA

EXCLUSION CRITERIA IECAT Check the appropriate response IETEST		**Yes**	**No**
1. Is pregnant, nursing, or planning to become pregnant within 6 months of last study treatment.	IEORRES when IETESTCD = EXCL01	☐	☐
2. Is unable or unwilling to undergo multiple venipunctures.	IEORRES when IETESTCD = EXCL02	☐	☐
3. Is known to have had a substance abuse (drug or alcohol) problem within the previous 3 years.	IEORRES when IETESTCD = EXCL03	☐	☐

*All **Exclusion Criteria** questions 1-3 must be answered **NO** to enter the study.*

DM=Demographics

CDISC
Study: CDISC01
STUDYID

Screening

Assessment Date

SCDTC _____/_____/_____

DEMOGRAPHY

Date of Birth: _____/_____/_ BRTHDTC

SEX

Gender: ☐ Male ☐ Female

ETHNIC

Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino

RACE

Race: Check all that apply

RACE, when more than one selected, RACE=MULTIPLE and individual responses are RACE1, RACE2, etc. in SUPPDM

☐ White
☐ American Indian or Alaska Native
☐ Black or African American
☐ Native Hawaiian or Other Pacific Islander
☐ Asian
☐ Other::__ RACEOTH in SUPPDM

SC=Subject Characteristics

SCORRES when SCTESTCD = MARISTAT

FamilyStatus: ☐ Never Married ☐ Domestic Partner
☐ Married ☐ Divorced
☐ Legally Separated ☐ Widowed

SCORRES when SCTESTCD = EDLEVEL

Education: ☐ Some High School ☐ College Graduate
☐ High School Graduate/GED ☐ Graduate Degree & Beyond
☐ Some College ☐ Other::____

EDUOTH in SUPPSC

DS=Disposition

INFORMED CONSENT DSDECOD

DSTERM

DSSTDTC

Date consent form signed: _____/_____/_____
MM DD YYYY

MH=Medical History

CDISC	Screening
	MHDTC
Study CDISC01	Assessment Date: ___/____/___

PSYCHIATRIC HISTORY *MHCAT*

MHTERM	*MHPRESP=Y*	*MHSTDTC*	*MHOCCUR=Y*
1. Date of onset of probable Alzheimer's Disease?		☐☐ ☐☐ ☐☐☐☐	
2. Date of onset of depression of Alzheimer's Disease?		☐☐ ☐☐ ☐☐☐☐	

MH=Medical History

CDISC Study CDISC01	SCREENING Assessment Date: MHDTC ___/___/___

MEDICAL AND SURGICAL HISTORY MHCAT

Does the subject have any significant medical or surgical history? [NOT SUBMITTED] ☐ Yes, list the condition(s) below ☐ No	Year MHSTDTC	"√" if RESOLVED MHENRF = BEFORE	"√" if ONGOING MHENRF = DURING/AFTER
MHTERM	☐☐☐☐		
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐
	☐☐☐☐	☐	☐

CM=Concomitant Medications

CDISC	SCREENING
	Assessment Date: _____/_____/_____

[NOT SUBMITTED]

PSYCHOTROPIC DRUG TREATMENT HISTORY

CMCAT

List all the Psychotropic drugs the patient has taken within the past 5 years.

If NONE, CHECK BOX: ☐ [NOT SUBMITTED]

Generic Drug Name (Enter the trade name for combination drugs)	Response Code	Total Daily Dose	Units	Start Date (M/D/Y)	Stop Date (M/D/Y)	Indication	Reason for Discontinuation
CMTRT		CMDOSTXT		CMSTDTC		CMINDC	
	PDRESP in SUPPCM		CMDOSU	/ /	CMENDTC		PDDREAS in SUPPCM
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		
				/ /	/ /		

Response Code
1 No Change
2 Poor
3 Good

Reason for Discontinuation
0 Ongoing
1 Adverse Event
2 Insufficient Response
3 Satisfactory Response
99 Other

PE=Physical Examination

CDISC Study CDISC01	PEDTC Assessment Date: _____/_____/_____

PHYSICAL EXAM

Note: If the result is Abnormal then PEORRES=Comment

PESTAT

PETEST PHYSICAL EXAM	Normal	Abnormal	Not Done	Comment only if abnormal
	PEORRES when PETESTCD=PE01			
1. Appearance/Skin	☐	☐	☐	
	PEORRES when PETESTCD=PE02			
2. Head/Neck (Including Thyroid)	☐	☐	☐	
	PEORRES when PETESTCD=PE03			
3. Eyes-Ears-Nose-Throat	☐	☐	☐	
	PEORRES when PETESTCD=PE04			
4. Cardiovascular	☐	☐	☐	
	PEORRES when PETESTCD=PE05			
5. Pulmonary	☐	☐	☐	
PEORRES when PETESTCD=PE06 6. Abdomen	☐	☐	☐	
PEORRES when PETESTCD=PE07 7. Neurological	☐	☐	☐	
PEORRES when PETESTCD=PE08 8. Musculoskeletal	☐	☐	☐	
PEORRES when PETESTCD=PE09 9. Other	☐	☐	☐	

VS=Vital Signs

CDISC Study: CDISC01	Assessment Date: VSDTC _____/_____/_____

VITAL SIGNS

VSTEST

Height ☐cm ☐ in

.

VSORRES / VSORRESU when VSTESTCD = HEIGHT

Weight ☐ kgs ☐ lbs

.

VSORRES / VSORRESU when VSTESTCD = WEIGHT

Body Fame Size ☐ Small ☐ Medium ☐ Large

VSORRES when VSTESTCD = FRMSIZE

VSPOS

Sitting Blood Pressure

/ mmHg

Systolic Diastolic

VSORRES / VSORRESU when VSTESTCD = SYSBP, DIABP

Radial Pulse Rate

bpm

VSORRES / VSORRESU when VSTESTCD = PULSE

LABORATORY

[NOT SUBMITTED]

Were laboratory tests performed at this visit? ☐ Yes ☐ No

EG=ECG

CDISC Study CDISC01	*EGDTC* Assessment Date: _____/_____/_____

12- LEAD ECG

ECG RESULTS

EGTEST

Ventricular Heart Rate	☐☐☐ bpm	*EGORRES / EGORRESU when EGTESTCD = VRMEAN*
PR Interval	☐☐☐ msec	*EGORRES / EGORRESU when EGTESTCD = PRMEAN*
QRS Interval	☐☐☐ msec	*EGORRES / EGORRESU when EGTESTCD = QRSDUR*
QT Interval:	☐☐☐ msec	*EGORRES / EGORRESU when EGTESTCD = QTMEAN*

EGTESTCD = INTP

OVERALL INTERPRETATION (Please check one):

1 = ☐ Normal (do not comment) *EGORRES = NORMAL*

2 = ☐ Abnormal, not clinically significant (do not comment) *EGORRES = ABNORMAL*
EGCLSIG=N in SUPPEG

3 = ☐ Abnormal, clinically significant. Specify and comment: *EGORRES = ABNORMAL*
Comments [char(200)]

EGCLSIG=Y in SUPPEG _____

EGCLSP in SUPPEG _____

_____

-

QS=Questionnaires

CDISC Study CDISC01	Assessment Date: _____/_____/_____ QSDTC

QSCAT **MINI-MENTAL STATE EXAMINATION (MMSE SUMMARY PAGE)**

Instructions: Please transcribe the appropriate scores from the MMSE workbook into the boxes below.

Rater's Initials: ☐☐☐ **RTRINIT in SUPPQS**

QSTEST

A. ORIENTATION

1. TIME: The range of scores is 0 to 5. **QSORRES when QSTESTCD = MMSEA1**

Score (total number of correct responses ☐

2. PLACE: The range of scores is 0 to 5. **QSORRES when QSTESTCD = MMSEA2**

Score (total number of correct responses ☐

B. REGISTRATION: The range of scores is 0 to 3. **QSORRES when QSTESTCD = MMSEB**

Score (total number of correct responses ☐

C. ATTENTION AND CALCULATION: The range of scores is 0 to 5. **QSORRES when QSTESTCD = MMSEC**

Score (total number of correct responses ☐

D. RECALL: The range of scores is 0 to 3. **QSORRES when QSTESTCD = MMSED**

Score (total number of correct responses ☐

E. LANGUAGE: The range of scores is 0 to 9. **QSORRES when QSTESTCD = MMSEET**

Score (total number of correct responses ☐

QSORRES when QSTESTCD = MMSETOT

Sum of Scores for Sections A through E ☐☐

QS=Questionnaires

CDISC Study CDISC01	QSDTC Assessment Date ____/____/____

CORNELL SCALE FOR DEPRESSION IN DEMENTIA (CSDD) (PAGE 1 OF 2)

QSCAT RTRINIT in SUPPQS

:

Instructions: For each item, select the "cue" which best characterizes the symptoms and signs occurring during the past week, and circle the appropriate number. QSEVLINT

Rater's Initials: ☐☐☐

QSSCAT		CUE		
A. MOOD - RELATED SIGNS		**ABSENT**	**MILD OR INTERMITTENT**	**SEVERE**
1. ANXIETY QSTEST Anxious expression, ruminations, worrying	QSORRES when QSTESTCD =CSDD01	0	1	2
2. SADNESS Sad expression, sad voice, tearfulness	QSORRES when QSTESTCD = CSDD02	0	1	2
3. LACK OF REACTIVITY TO PLEASANT EVENTS	QSORRES when QSTESTCD = CSDD03	0	1	2
4. IRRITABILITY Easily annoyed, short tempered	QSORREswhen QSTESTCD = CSDD04	0	1	2
B. BEHAVIORAL DISTURBANCE				
5. AGITATION Restlessness, handwringing, hairpulling	QSORRES when QSTESTCD = CSDD05	0	1	2
6. RETARDATION Slow movements, slow speech, slow reactions	QSORRES when QSTESTCD = CSDD06	0	1	2
7. MULTIPLE PHYSICAL COMPLAINTS (score 0 if GI symptoms only)	QSORRES when QSTESTCD = CSDD07	0	1	2
8. LOSS OF INTEREST Less involved in usual activities (score only if change occurred acutely, i.e. in less than 1 month)	QSORRES when QSTESTCD = CSDD08	0	1	2

QS=Questionnaires

CDISC Study CDISC01	QSDTC Assessment Date: _____/_____/_____

CORNELL SCALE FOR DEPRESSION IN DEMENTIA (CSDD) (PAGE 2 OF 2)

QSCAT

QSSCAT C. PHYSICAL SIGNS	CUE ABSENT	MILD OR INTERMITTENT	SEVERE
9. APPETITE LOSS QSTEST Eating less than usual	QSORRES when QSTESTCD = CSDD09 0	1	2
10. WEIGHT LOSS (score 2 if greater than 5 lbs. in 1 month)	QSORRES when QSTESTCD = CSDD10 0	1	2
11. LACK OF ENERGY Fatigues easily, unable to sustain activities (score only if change occurred acutely, i.e., in less than 1 month)	QSORRES when QSTESTCD = CSDD11 0	1	2
D. CYCLIC FUNCTIONS			
12. DIURNAL VARIATION OF MOOD Symptoms worse in the morning	QSORRES when QSTESTCD = CSDD12 0	1	2
13. DIFFICULTY FALLING ASLEEP Later than usual for this individual	QSORRES when QSTESTCD = CSDD13 0	1	2
14. MULTIPLE AWAKENINGS DURING SLEEP	QSORRES when QSTESTCD = CSDD14 0	1	2
15. EARLY MORNING AWAKENING Earlier than usual for this individual	QSORRES when QSTESTCD = CSDD15 0	1	2
E. IDEATIONAL DISTURBANCE			
16. SUICIDE Feels life is not worth living, has suicidal wishes, or makes suicide attempt	QSORRES when QSTESTCD = CSDD16 0	1	2
17. POOR SELF-ESTEEM Self-blame, self-depreciation, feelings of failure	QSORRES when QSTESTCD = CSDD17 0	1	2
18. PESSIMISM Anticipation of the worst	QSORRES when QSTESTCD = CSDD18 0	1	2
19. MOOD-CONGRUENT DELUSIONS Delusions of poverty, illness, or loss	QSORRESwhen QSTESTCD = CSDD19 0	1	2

Reminder: The patient must have a minimum total score of 13 on the CSDD at both Screening and Baseline visits to be eligible for study participation.

QSORRES when QSTESTCD = CSDDTOT

Total Score: ☐☐

DS=Disposition

CDISC	
Study CDISC01	

RANDOMIZATION

DSTERM / DSDECOD = RANDOMIZED

DM=Demographics

RANDNO in SUPPDM

Will the patient be randomized? ☐ **Yes** Enter Randomization Number ☐☐☐☐

RAND in SUPPDM

Randomization Date ☐☐ ☐☐ ☐☐☐☐
MM DD YYYY

DSSTDTC

☐ **No** Complete Termination

QS=Questionnaires

CDISC **Study CDISC01**	***QSDTC*** **Assessment Date _____/_____/_____**

QSCAT **CLINICAL GLOBAL IMPRESSION (CGI-I)**

RTRINIT in SUPPQS

Rater's Initials: ☐☐☐

QSTEST

GLOBAL IMPROVEMENT

Rate total improvement or worsening relative to baseline with respect to the patient's Disease. Compared to his/her condition at baseline, how much has the patient changed?

QSORRES when QSTESTCD = CGIGLOB

1 ☐ Very much improved

2 ☐ Much improved

3 ☐ Minimally improved

4 ☐ No change

5 ☐ Minimally worse

6 ☐ Much worse

7 ☐ Very much worse

DS=Disposition

CDISC

Study CDISC01

Assessment Date: _____/_____/_____

[NOT SUBMITTED]

TERMINATION

Did patient complete the study? ☐ Yes ☐ No

DSDECOD / DSTERM = COMPLETED when Yes

If patient did not complete the study, indicate the date of termination and check one primary reason to indicate why:

Date of Termination: ☐☐/☐☐/☐☐☐☐ ***DSSTDTC***

DSDECOD

☐ Patient did not meet Inclusion/Exclusion Criteria at Screening or baseline (specify): : ***DSTERM*** _____

_____

☐ Discontinued due to lack of Therapeutic Response ***DSDECOD***

☐ Discontinued due to Adverse Event

Adverse Event No. _____ (Enter the number from the ADVERSE EVENTS Form)

Linked to related AE record via RELREC

☐ Protocol Violation (specify) : ***DSTERM*** _____

☐ Discontinued due to Consent Withdrawn

☐ Discontinued due to Lost to Follow Up

☐ Discontinued due to Sponsor/Investigator Decision, specify: ***DSTERM*** _____

I have reviewed the data associated with the case report forms for this subject and have determined that the data are accurate and are consistent with supporting source documentation.

Investigator's Signature: _____ Date: _____/_____/_____

Investigator's Name: _____

DA=Drug Accountability

CDISC Study CDISC01	STUDY MEDICATION INVENTORY

Date Tablets Dispensed	Number of Tablets Dispensed	Date Tablets Returned	Number of Tablets Returned
DADTC when DATESTCD=DISPAMT	DATEST DAORRESU DAORRES when DATESTCD=DISPAMT	DADTC when DATESTCD=RETAMT	DATEST DAORRESU DAORRES when DATESTCD=RETAMT
☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐	☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐
☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐	☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐
☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐	☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐
☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐	☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐
☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐	☐☐ ☐☐ ☐☐☐☐ Month Day Year	☐☐

EX=Exposure

CDISC Study CDISC01	Medication Record

EXDOSFRM

Please record the total number of tablets taken for the consecutive days that the patient received that dose.

From			To			Number of Tablets per Day
Month	Day	Year	Month	Day	Year	
EXSTDTC			EXENDTC			SMNO in SUPPEX

AE=Adverse Events

	CDISC Study CDISC01	

ADVERSE EVENTS

			Relation to Study Drug			Maximum Intensity			Action Taken				Serious Adverse Event?		Resolution (Complete One)	
		AESTDTC	AEREL			AESEV			AEACN				AESER		AEENDTC	AEENRF = AFTER
AE No.	Adverse Event	Onset Date (MM/DD/YY)	Not Related	Possibly Related	Related	Mild	Moderate	Severe	Dose Not Changed	Dose Reduced	Drug Interrupted	Drug Withdrawn	Yes	No	Resolution Date (M/M/DD/YY)	Ongoing
AESPID	AETERM	/ /	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	/ /	☐
		/ /	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	/ /	☐
		/ /	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	/ /	☐
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		/ /	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	/ /	☐

If one or more serious outcomes are reported, notify a sponsor IMMEDIATELY.

CM=Concomitant Medications

CDISC

Study CDIOSC01

PRIOR / CONCOMITANT MEDICATIONS CMCAT

Medication	Start Date (M/D/Y) CMSTDTC	Stop Date (M/D/Y) CMENDTC	Continuing CMENRF = AFTER	Dose CMDOSTXT	Unit CMDOSU	Route CMROUTE	Frequency	Indication CMINDC
CMTRT	/ /	/ /	☐				CMDOSFRQ	
	/ /	/ /						
	/ /	/ /	☐					
	/ /	/ /	☐					
	/ /	/ /	☐					
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	/ /	/ /	☐					
	/ /	/ /	☐					
	/ /	/ /	☐					

CLINICAL TRIAL PROTOCOL

Compound: **Amphinex**

Protocol code: **PCI 101/06**

EudraCT number: **2006-005106-30**

Protocol title: **An open, phase I, dose-escalating study to evaluate the safety and tolerance of Amphinex based Photochemical Internalisation (PCI) of bleomycin in patients with local recurrence or advanced/metastatic, cutaneous or sub-cutaneous malignancies.**

Protocol date/status: 08 March 2010 / FINAL PROTOCOL WITH AMENDMENT 12

University College London Hospital:
Coordinating Investigator: Mr Colin Hopper, MD
University College London Hospital
Head and Neck Centre
1st Floor East
250 Euston Road
London NW1 2PG, UK

SPONSOR

Research Director
Anders Høgset,
PCI Biotech AS

Sign: _____

Date: _____

BIOSTATISTICIAN

Senior Statistician
Trond Haider
Link Medical Research AS

Sign: _____

Date: _____

Protocol Authors

Mariann Jeremiassen, Cand. Scient., PCI Biotech AS
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Ole-Jacob Norum, MD, Radiumhospitalet
Even Angell-Petersen, Ph D, Radiumhospitalet

CONFIDENTIALITY STATEMENT

I agree to perform this trial, to maintain the procedures required to carry it out and -to abide by the terms of this protocol. This clinical trial protocol is confidential and the property of PCI Biotech AS and may not be used, disclosed or published without their consent.

Signature of coordinating investigator:

Mr Colin Hopper, MD
University College London Hospital
l Head and Neck Centre

Sign: _____

Date: _____

PROTOCOL SYNOPSIS

Product: 4 ml Amphinex 30 mg/ml solution for injection

Study title: An open, phase I, dose-escalating study to evaluate the safety and tolerance of Amphinex based Photochemical Internalisation (PCI) of bleomycin in patients with local recurrence or advanced/metastatic, cutaneous or sub-cutaneous malignancies.

Centres: This study will be performed at one centre.

Key dates:
Anticipated start of patient recruitment: 2Q 2009
Anticipated end of patient recruitment: 1Q 2010
Anticipated end of patient follow-up: 3Q 2010

Primary Objective: To assess the safety and tolerance of the Amphinex and determine the maximal tolerated dose (MTD) of Amphinex in Amphinex based PCI of bleomycin.

Secondary Objective: To evaluate the toxicity, including skin photosensitivity of Amphinex in Amphinex based PCI of bleomycin.

To determine the pharmacokinetics of Amphinex in Amphinex based PCI of bleomycin.

To document antitumor activity observed with Amphinex in Amphinex based PCI of bleomycin.

Study design: This study is an open, non- randomized, phase I, dose-escalating study to evaluate the safety and tolerance of Amphinex based PCI of bleomycin in patients with local recurrent or advanced/metastatic, cutaneous or sub-cutaneous malignancies.

Eligible patients will be included in cohorts of 3 patients. The initial starting dose for Amphinex will be 0.25 mg/kg, administered as a slow intravenous injection of 1-6 minutes at day 0, given 4 days prior to the fixed dose of 15000 IU/m^2 bleomycin administered by intravenous infusion. No Amphinex dose will exceed 3 mg/kg bodyweight. If a situation arises where no DLT is seen in at least 3 consecutive dose groups, including the starting dose of 0,25 mg/kg, and efficacy is demonstrated in the same dose groups, the dose escalation

committee may decide to lower the Amphinex dose below the starting dose of 0.25 mg/kg. The illumination, with red light (laser 652 nm), fixed dose of 60 J/cm², delivered at an irradiance of 100 mW/cm^2 to the tumour surface and a margin of 2-3 mm outside the tumour surface, implying an illumination time of approximately 600 seconds**,** will be performed within a time window of 3 hours (+/- 30 minutes) after bleomycin administration.

There will be no comparative procedure in this study.

Dose escalation will proceed according to a modification of Simon's accelerated titration design. The number of patients recruited depends on the DLT experienced. A total of 6 patients will be included at each dose level if no more than 1 patient experiences DLT.

Additional cohorts may be added pending the outcome of the previous cohorts and discussions between the investigators and the Sponsor. The primary goal of the study is to assess the safety and tolerance of the Amphinex and determine the maximal tolerated dose (MTD) of Amphinex as a PCI therapy in combination with bleomycin treatment.

The discontinuation of a patient from the study will occur in the event of disease progression or dose limiting toxicity (DLT).

Target

Population: Patients with the following diagnosis will be targeted for this study:

- Cutaneous breast cancer metastases and local recurrence, verified by cytology test.
- Squamous cell carcinomas (both head and neck, including oral cavity and pharynx, and non-head and neck), local recurrence, verified by cytology test.

Safety: An assessment of all adverse events experienced since treatment visit and assignment of CTCAE grades to all those considered to be drug related will be done at all visits. Adverse events will be followed until resolved. Blood sampling to check standard blood biochemistry and vital signs will be performed. Fluorescence and skin photosensitivity will be measured and followed until values are returned to normal values.

Study duration: Patient enrolment is estimated to take 18 months, patient treatment and follow-up 3 months, with a total of 21 months.

LIST OF ABBREVIATIONS

AE	Adverse Event
CPMP	Committee for Proprietary Medicinal Products
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events v 4.0
CV	Curriculum Vitae
CRO	Clinical Research Organisation
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
DLT	Dose Limiting Toxicity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
IU	International unit
ICH	International Conference of Harmonisation
IRB	Institutional Review Board
J	Joule
mW	milliwatt
min	minutes
MRI	Magnetic Resonance Imaging
nm	nanometer
PDT	Photodynamic Therapy
PCI	Photochemical Internalisation
PS	Photosensitiser
RBC	Red Blood Cell Count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
sec	Seconds
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SAP	Statistical Analysis Plan
VAS	Visual Analogue Scale
WBC	White Blood Cell Count

All dimensional units are in standard SI units.

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1. INTRODUCTION

Cancer causes more than 8 million deaths each year, or approximately 13 percent of all deaths worldwide [1]. Advanced or metastatic cancer is ranking second only to cardiovascular disease as an overall cause of mortality. Therefore it is crucial to continue to develop new and effective treatments and to improve the efficacy of the treatments that are already in use.

In this study we will use the well established chemotherapeutic agent bleomycin in combination with a novel technology, photochemical Internalisation (PCI), developed to improve the effect of anti-cancer therapeutics. In the study the safety and tolerability of the newly developed photosensitiser Amphinex in the treatment of cancers on the body surface will be explored.

1.1 Photodynamic therapy (PDT)

The principle of photodynamic therapy (PDT) is to selectively destruct neoplastic cells, like cancer cells, by light activation of a photosensitising compound (a photosensitiser) in the presence of oxygen.

The therapeutic effect of PDT may be due to direct cell killing and/or vascular damage, but there are also indications that immune responses may be of importance. Thus, although PDT is a local treatment modality there is substantial preclinical evidence for the importance of both the innate and acquired immune system for the therapeutic effects [2].

The importance of immune responses in PDT depends both on the photosensitizer and its formulation, the way of administration and the time between administration of the photosensitizer and exposure to light. In this study the possible cancer vaccination effects of photochemical treatment with Amphinex will be evaluated.

The importance of T-cells for the PDT response has been shown by the increased anti-tumour effect of PDT in immunocompetent mice as compared to athymic mice [3]. Furthermore, an increased PDT treatment effect has been observed by administration of T-cells to athymic mice [3-4]. The vaccinating effect of PDT is indicated by the limited growth of tumours in syngeneic mice after repeated administration of PDT-killed tumour cells prior to the injection of viable tumour cells [5], inhibition of growth of new tumours in mice previously cured by PDT [6], and by the reduced growth of tumours when PDT-killed tumour cells are injected peritumorally [7]. Preliminary results indicate similar responses to PDT with Amphinex.

The importance of immune responses are further strengthened by the tumour growth inhibitory effects of immature dendritic cells injected into photodynamically treated tumours. Injection of such cells gives growth inhibition on distant tumours not treated with PDT [8], and also reduces the number of lung metastases after i.v. injection of tumour cells [9]. Clinically, there is less documentation of the vaccinating effect of PDT. However, in a study of PDT on vulval intraepithelial neoplasia (VIN) a significant increase in CD8+ T-cell infiltration was observed in the treatment responders as compared to the non-responders [10]. The PDT non-responders were also more likely to show HLA class I loss compared to the responders.

In addition, in contrast to surgery, radiotherapy and chemotherapy that are mostly immunosuppressive, PDT causes acute tumour inflammation, with expression of heat-shock proteins and various immuonstimulatory cytokines, invasion and infiltration of leukocytes [2].

1.2 Photochemical Internalisation (PCI)

Photochemical Internalisation (PCI) is a novel photochemical technology. PCI combines PDT with a therapeutic molecule. The application of PCI in combination with a therapeutic molecule enhances the effect of the therapeutic molecule.

It might be anticipated that PCI will have the same immunostimulatory effects as PDT treatment, and the same advantages as PDT treatment over surgery and radiotherapy. The PCI effect is induced by light doses that only kill a low fraction of cells. In the cells that are not killed by the illumination, the light will induce the release of the therapeutic molecule from the endocytic vesicles. The therapeutic molecule, if it's a cytotoxic agent, then kills the cells. This added effect of PCI makes the light doses needed for a therapeutic effect with PCI substantially lower than those needed in PDT. This may also allow PCI to efficiently treat thicker lesions than what is possible with PDT [11, 12].

A common feature of candidate therapeutic molecules that may be used in PCI is that they have an intracellular target for the anti-carcinogenic action. Many drug targets are located intracellular, including the most important current targets for cytotoxic anti-cancer therapy. Cellular uptake may however be very limited for several important classes of therapeutic molecules that will not readily pass the plasma membrane. One way such molecules could anyway be taken up by the cells is by endocytosis; however, for most existing and potential therapeutics molecules this pathway leads to degradation and loss of the biological activity of the therapeutic molecules before these have been able to reach their intracellular drug targets.

In the PCI technology, the photosensitiser Amphinex is used for improving the release of endocytosed therapeutic molecules into the cytosol. Initially inserted into the plasma membrane, Amphinex is then internalised by endocytosis and ends up in the membranes of endocytic vesicles within the cell [13]. When Amphinex is exposed to light of certain wavelengths, the membrane of the endocytic vesicles is disrupted and the vesicular contents, including the therapeutic molecules, will be released into the cytosol [14, 15].

Ideally, a candidate molecule for use with PCI should only be active in cells that are illuminated, and should only give very limited adverse effects on non-illuminated cells and tissues. This is in contrast to other drugs that are generally membrane permeable, like many current cancer cytotoxic agents. These drugs will generally be taken up by and be active also in non-target cells. This often generates severe side effects like oedema, febrile neutropenia, thrombocytopenia, etc. [11].

It is of great interest to be able to improve the biological effect and lower the toxicity of anti-cancer treatments. This is the first study where the possibility to use PCI in patients to improve the performance of approved anti-cancer drugs is investigated.

1.3 Pre-clinical Experience with PCI and Amphinex

PCI combining Amphinex and bleomycin constitutes a site-specific treatment very well suited for local tumor treatment. In animal models, PCI with Amphinex and bleomycin give statistically significant improved therapeutic effects as compared to the effects of PDT alone (both temoporfin and Amphinex), and the effects of bleomycin alone [16, 19].

The toxicity and side effects of Amphinex treatment seems acceptable, based on the data generated in Amphinex animal studies and also based on what can be inferred from the clinical experience with other photosensitisers. There is no sign of skin photosensitivity 14 days after photosensitiser administration to mice [16].

In general, the combination of Amphinex and bleomycin in animal studies show an synergistic tumor response as determined by tumor growth delay (duration of response) or increase-in-lifespan (survival). Amphinex has proven to be effective and safe in these in vivo models. These pre-clinical data indicate that Amphinex is a good candidate for combinational therapies with chemotherapy agents and warrants further studies in human cancers.

1.4 Rationale for Investigation of Amphinex in combination with bleomycin

Bleomycin is approved and in clinical use in the treatment of squamous cell carcinomas of the head and neck, esophagus, bronchus and skin, as well as testis cancer and malignant lymphomas. However, the sensitivity of tumour cells to bleomycin is highly variable, at least partly due to a limited intracellular uptake in the target cells [17], but it is known that bleomycin can be quite efficiently taken up by endocytosis [18]. Bleomycin should thus be an excellent drug for increased cellular uptake induced by PCI. In line with this, *in vitro* and *in vivo* studies have shown that PCI can substantially enhance the therapeutic effect of bleomycin [19].

Clinical studies have shown that when bleomycin is administered in combination with electroporation, its effectiveness as an antitumor agent is greatly enhanced [20-23]. It has been estimated that as little as ~ 500 bleomycin molecules translocated into the cytoplasm may be sufficient to kill a cell [24]. In addition, in pre-clinical studies, the therapeutic response indicates that PCI treatment may present a way to significantly increase the efficacy of bleomycin treatment, and thereby reduce the therapeutic dose of bleomycin. The risk of developing pneumonitis and fatal lung fibrosis is dose-dependent and correlates with the total accumulated dose of bleomycin [25]. One treatment session with bleomycin in combination with PCI may be sufficient for the achievement of a good therapeutic response [19]. Fewer treatments and a lower dose of bleomycin are expected to give less adverse events for the patient. PCI may also limit the need for supportive treatment and give the patient an improved quality of life. Bleomycin will be the first substance to be used in clinical studies with PCI. One treatment session will be employed, since this was shown to be efficient in the animal studies.

1.5 Patient Selection and ethical consideration

Patients with advanced or metastatic, cutaneous or sub-cutaneous malignancies, including head and neck, will be eligible for this study. The patients will be informed about the opportunity to participate in this trial, and before any trial-related procedures are performed,

the patient must be thoroughly informed about the study verbally and in writing and he/she must also sign and date the informed consent form.

The clinical trial will be conducted in compliance with the protocol, according to ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95, and national guidelines including Clinical Trials Directive 2001/20/EC, Code of Federal Regulations Title 21, and Guideline on the Evaluation of Anticancer Medicinal Products in Man, CPMP/EWP/205/95/Rev.3/Corr

2. OBJECTIVES OF THE TRIAL

2.1 Primary Objective

To assess the safety and tolerance of the Amphinex and determine the maximal tolerated dose (MTD) of Amphinex in Amphinex based PCI of bleomycin.

2.2 Secondary Objective

To evaluate the toxicity, including skin photosensitivity of Amphinex in Amphinex based PCI of bleomycin.

To determine the pharmacokinetics of Amphinex in Amphinex based PCI of bleomycin.

To document antitumor activity observed with Amphinex in Amphinex based PCI of bleomycin.

3. INVESTIGATIONAL TRIAL DESIGN

3.1 Design

An open, non- randomized, phase I, dose-escalating study to evaluate the safety and tolerance of Amphinex based PCI of bleomycin in patients with local recurrent or advanced/metastatic, cutaneous or sub-cutaneous malignancies.

There will be no comparative procedure in this study.

Dose escalation will proceed according to a modification of Simon's accelerated titration design [26].

For Study Flow Chart, see **Appendix B**.

3.2 Primary Endpoint

Establish the dose limiting toxicity (DLT) of Amphinex defined as the dose level at which 33% of the patients within a cohort experiences unacceptable toxicity (DLT).

3.3 Description of Investigational Drug

Amphinex is supplied in vials. The strength is given as the concentration of the active entity, Amphinex. The color of the solution is purple.

3.4 Drug Labelling

Labelling will be performed in the local language and following local guidelines. As a minimum the below mentioned information will be included.

Text for UK site:
Outer packaging:

"FOR CLINICAL TRIAL USE ONLY"

Study: PCI 101/06

4 ml Amphinex 30 mg/ml fluid for injection
for slow i.v. injection.

Dose: .....

Subject no. .....
Batch no. XXX
Expiry date: XXX
Store in outer packaging at 2-8^{o}C. Shake before use.
Responsible physician: Dr…….
Hospital: University College London Hospital, London
Sponsor: PCI Biotech AS, Hoffsveien 48, N-0377 Oslo, Norway
Tel: +47 23 25 40 03

Immediate container:
Study: PCI 101/06. Subject no: …….
4 ml Amphinex 30 mg/ml fluid for i.v. injection. Dose: …….
Batch no: XXXX
Sponsor: PCI Biotech AS, Hoffsvn. 48,
0377 Oslo, Norway. Tel: +4723254003

3.5 Drug Ordering and Storage

The Norwegian Institute of Public Health manufactures Amphinex. The shipment of the vials will be addressed to the hospital pharmacy, where the vials will be stored in the outer package, at 2-8°C. Storage temperature will be monitored and recorded in a log.

PCI Biotech AS will supply Amphinex and Bleomycin Baxter 15 000 IE for the study.

3.6 Investigational Light Source

The light source used in this study is a Ceralas PDT 652+/-3nm 2W" by CeramOptec GmbH (Bonn, Germany, CE0297) laser that emits red light at 652 nm.

3.7 Dosage and Administration

All patients in this study will receive Amphinex and illumination in combination with a fixed dose bleomycin. Amphinex and bleomycin will be administered intravenously.

The initial starting dose of Amphinex will be 0.25 mg/kg, given as a slow intravenous injection over 1-6 minutes, into a vein not distal to the antecubital fossa, at day 0. Following the Amphinex injection, the vein catheter (e.g. Venflon) will be flushed with physiologic saline solution in the order to ensure that the study drug is flushed from the injection site.

Amphinex doses will not exceed 3 mg/kg.

Bleomycin, 15 000 IU/m^2, will be given as an infusion at 1 000 to 1 500 IU/minute at day 4, i.e. over 10-15 minutes.

The patient will be observed for a minimum of 2 hours following both Amphinex and Bleomycin administration.

The illumination will be performed using a laser within a time window of 3 hours (+/- 30 minutes) after bleomycin administration. Red light (652 nm) at a fixed dose of 60 J/cm^2, delivered at an irradiance of 100 mW/cm^2 will be delivered to the tumour surface and a margin of 2-3 mm outside the tumour surface. Thus, an illumination time of approximately 600 seconds is necessary**.**

The tumour surface is defined as the measurable lesion.

3.8 Definition of Maximum Tolerated Dose

In this study, the maximum tolerated dose (MTD) of Amphinex is defined as the dose level at which 33 % of patients within a cohort experiences unacceptable toxicity (dose limiting toxicity, see below). Dose selection for future Phase 2 studies will be based on these data.

The patients in this study will receive site-specific treatment (illumination). It is only in the areas of the body that are illuminated that the major anti-tumour activity is expected and reactions will be seen in the treatment area as a consequence of the anti-tumour activity. Based on this a higher grade of toxicity will be accepted inside the illuminated area. It is to the discretion of the responsible investigator to decide when the dose of Amphinex is sufficient for lesion treatment, depending on the well-being of the patient and the location of the lesion. If this level is reached without obtaining dose limiting toxicities (DLT), then a revised dose escalation schema will be made based on a consensus between the investigators and the sponsor. In this special case it may be relevant to consider continuing the Amphinex dose escalation according to the protocol but reducing the light dose in order to avoid unacceptable effects due to over-treatment of the illuminated area.

When the patient experiences any unacceptable toxicity, this will be defined as DLT.

The DLT is defined as:

- Photosensitivity grade 2 outside the illuminated area as defined in the Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) (see Appendix F), except for areas exposed for skin sensitivity tests and areas exposed for re-introduction to normal light.
- Photosensitivity grade 4 inside the illuminated area as defined in CTCAE
- Pneumonitis grade 3 as defined in CTCAE
- Nonhematologic toxicity (excluding nausea and vomiting) $\geq$ grade 3 as defined in CTCAE
- Neutropenia or thrombocytopenia grade 4 as defined in CTCAE
- All other toxicity reactions of $\geq$ grade 3 as defined in CTCAE

3.9 Dose escalation between cohorts

Upon confirmation of eligibility, the sponsor will inform the site which dose level the patient will receive.

The patients who receive the same dose level form a cohort.

General description: The initial starting dose of Amphinex will be 0.25 mg/kg. Dose escalation will proceed according to a modification of Simon's accelerated titration design [26]. Dose levels will be doubled until study drug related grade 2 toxicity in 1 patient during treatment is observed. If this is the case, subsequent dose levels will be escalated at 1.5 times the preceding dose level until a study drug related grade 2 is noted in at least 2 patients. Once a study drug related grade 2 toxicity in at least 2 patient during treatment is noted, dose escalation will proceed at 1.3 times the previous dose level until dose-limiting toxicity (DLT) is identified. If the first study drug-related toxicity is grade 3 or greater, no dose level will be escalated at 1.5 times the preceding dose, but instead a dose level will be escalated at 1.3 times the preceding dose.

Amphinex dose levels shall not exceed 3 mg/kg bodyweight.

Examples: If no study drug-related toxicity is observed, the dose escalation levels per dose level will be 0.25 mg/kg, 0.5 mg/kg, 1.0 mg/kg etc. If grade 2 toxicity is seen within the first dose level, then the second dose level will be 0.37 mg/kg. If no more toxicity is experienced, the subsequent dose levels will be 0.56 mg/kg, 0.84 mg/kg etc. If the second dose level is 0.37 mg/kg and grade 2 toxicity is experienced (and after this no more toxicity), subsequent dose levels would be 0.48 mg/kg, 0.62 mg/kg, 0.81 mg/kg etc. If grade 3 toxicity is seen within the first dose level, then the second dose level will be 0.33 mg/kg. In case of no more toxicity the following dose level will be 0.42 mg/kg, 0.55 mg/kg, 0.72 mg/kg etc.

Dose escalation will be stopped when > 33% of the patients at a given dose level report DLT within 29 days after treatment. If the dose of Amphinex sufficient for lesion treatment is reached without obtaining DLT, the dose escalation will be stopped. A revised dose escalation schema will be made based on a consensus between the investigators and the sponsor. In this special case it may be relevant to consider continuing the Amphinex dose escalation according to the protocol but reducing the light dose in order to avoid unacceptable effects due to over-treatment of the illuminated area. If a situation arises where no DLT is seen in at least 3 consecutive dose groups, including the starting dose of 0,25 mg/kg, and efficacy is demonstrated in the same dose groups, the dose escalation committee may decide to lower the Amphinex dose below the starting dose of 0.25 mg/kg. If a patient included in such a low dose group has no signs of therapeutic effect 28 days after treatment, then he or she may be offered a second treatment with Amphinex PCI of bleomycin at an Amphinex dose of 0.5 mg/kg bw or an alternate therapy decided by the investigator.

The investigators and the sponsor should discuss and consent before starting a new dose level in order to ensure patient safety. The decision will be communicated to the appropriate site personnel.

A committee will be established to determine the next dose level. The committee will be chaired by the Coordinating Investigator, who has the final say in case of disagreement. Other committee members will be sub-investigators and a study nurse from UK, a representative from PCI Biotech and study statistician from Link Medical Research. The committee will be summoned by the PCI representative, so that they have a telephone conference when the results from one cohort (3 patients followed through day 14, including lab results) are known, verified and entered in a locked database. Normally dose escalation will occur as described in the protocol **3.9 dose escalation between cohorts** and **3.10 dose escalation within cohorts,** but the committee may decide to revise the dose escalation based on occurrence of side effects, pharmaco-kinetic results, and/or efficacy results.

A responsible person from Link Medical Research will be appointed to keep track of the inclusion process. This person should be in close contact with the site, and shall keep investigators, study nurses, PCI and LINK Medical updated on inclusion, when to and when not to include new patients.

Dose, dose interval, and dose escalation levels may be modified during the course of this study based on frequent cohort analysis of pharmacokinetics and safety data from low dose levels.

The investigators and the sponsor will review the data and select an appropriate dose level for subsequent efficacy trials. This dose will be determined by considering overall toxicity, pharmacokinetic data, and efficacy results. A minimum of 6 additional patients will be treated at this dose.

3.10 Dose Escalation within cohorts

A minimum of 3 patients will be treated at each new dose level. A maximum of 6 patients may be treated at one dose level if no more than one patient experiences DLT according to the schedule described below. After 1 patient at a given dose level has been treated, safety data will be reviewed by the investigators and the sponsor. If the first patient has not experienced DLT in the first 14 days after treatment, an additional 2 patients will be treated at that dose level to confirm the safety and toxicity of the drug. Once the first patient in the cohort has been without DLT 28 days after treatment and the next 2 patients within that cohort have been without DLT 14 days after treatment, the next higher dose level can begin accrual.

If the initial patient experiences DLT during the first 14 days after the treatment, then that patient will be observed for 28 days prior to enrolling additional patients at that dose level. If one of the first 3 patients experience DLT within a dose level, a total of 6 patients will be treated at that dose level. The additional 3 patients may be enrolled simultaneously. If 2 or more of these 6 patients experience DLT, then dose escalation will cease. Thus, if > 33% of patients at a given dose level report DLT within the first 29 days after treatment, accrual for that dose level will cease and dose escalation will be stopped, and the MTD will have been exceeded. If 33 % of patients at a given dose level report DLT, the MTD will have been reached. Following discussions between the investigators and sponsor, additional patients may be treated at intermediate doses between the previous dose level and the MTD level.

3.11 Concomitant Therapy

No other chemotherapy, immunotherapy, anticancer hormonal therapy, or experimental medications are permitted during the first 28 days of the study. In addition, any disease progression requiring other forms of specific antitumor therapy, except pre-planned excision of tumor, will also necessitate early discontinuation from the study.

The patients should be pre-treated with steroids and antihistamines (H1 +H2 inhibitors) to prevent anaphylactic reactions due to Cremophor, and observed for the first 30 minutes following the start of the infusion. If the patient experiences severe adverse reactions due to light exposure after receiving Amphinex, follow hospital standard treatment.

Appropriate documentation for all forms of pre-medications, supportive care, and concomitant medications is captured in the case report form (CRF).

3.12 Study Duration

All patients will receive one dose of Amphinex and bleomycin, on day 0 and 4 respectively. In addition, the patients will be seen maximum at visits at day 1, 2, 3, 5, 6, 7, 9, 11, 14, 21, 28 and at 3 months.

3.13 Drug Accountability

The study medication will be kept secure and at limited access, and will only be supplied to patients in the trial under the supervision of the Investigator. The Investigator is responsible for the drug accountability and maintaining accurate records of the dispensing of study medication. Used glass bottles have to be returned to the pharmacy. The Amphinex vials can only be stored in room temperature for 24 hours and has to be returned to the pharmacy within this time period. Used glass bottles will be stored at 2 - 8°C to the finalization of the clinical trial and the compilation of the final report. Then it will be returned to the Norwegian Institute of Public Health. The monitor will audit the drug accountability at the pharmacy during the monitoring visits.

Any study medication accidentally or deliberately destroyed will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

Administration of study medication to the patient will be carried out at the hospital and provision will be made in the CRF for the Investigator to verify that dosing has taken place in accordance with this protocol.

3.14 Source Data Identification

Patient information collected in the CRF, but not recorded in the hospital journal (patient notes), is regarded as source data. However, data such as visit dates, safety data including AE's and serious adverse events (SAE's), and patients consent withdrawal should always be recorded in the hospital journal (patient notes) and in the CRF's. The hospital journal (patient notes) should also state that the patient is participating in this clinical trial.

4. PATIENT SELECTION

4.1 Number of Patients and Target Population

PCI, using Amphinex in combination with bleomycin may be an alternative treatment modality for patients with local recurrence or advanced/metastatic, cutaneous or sub-cutaneous malignancies who have failed previous therapies.

Patients with the following diagnosis will be targeted for this study:

- Cutaneous breast cancer metastases and local recurrence, verified by cytology test.
- Squamous cell carcinomas (both head and neck, including oral cavity and pharynx, and non-head and neck), local recurrence, verified by cytology test.

The number of patients recruited depends on the DLT experienced. A total of 6 patients will be included at each dose level if no more than 1 patient experiences DLT.

4.2 Patient Screening

Patients fulfilling the inclusion criteria will be informed about the possibility of participation in this study.

Before any trial related procedures are performed, the patient must be thoroughly informed, both verbally and in writing; about the study and he/she will be given the opportunity to ask questions. The patient will then sign and date the informed consent form. Medical history of the patient will be recorded.

4.3 Inclusion Criteria

Patients may be included in the study if they meet **all** of the following criteria:

- Male or female aged 18 years or above who have given written informed consent.
- Skin type I- IV according to the Fitzpatrick skin classification (see appendix G).
- With a diagnosis of local recurrence or advanced/metastatic, cutaneous or subcutaneous malignancy
- Lesion measurement must not be done more than 2 weeks before the beginning of treatment. More than one field with lesion can be illuminated, but care must be taken to avoid overlap of the fields illuminated.
- Have discontinued any other investigational therapy or radiotherapy for at least 2 weeks prior to administration of Amphinex at the baseline visit, and have recovered from the acute effects of therapy.
- Have discontinued cytostatic or cytotoxic therapies with at least 6 half life cycles of the agent prior to administration of Amphinex at the baseline visit.
- Have a performance status of 0-2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see appendix D).
- Clinically assessed as eligible for bleomycin chemotherapy.
- Have a predicted life expectancy of at least 3 months.
- Geographic proximity that allow adequate follow-up.

- If female: have had childbearing potential either terminated by surgery, radiation, or menopause or attenuated by the use of an approved contraceptive method during and for 3 months after the trial.
- If male: have had reproductive potential either terminated or attenuated by the use of an approved contraceptive method during and for 3 months after the trial.

4.4 Exclusion Criteria

Patients will be excluded from the study for **any** of the following reasons:

- Have received prior PCI.
- Tumours known to be eroding into a major blood vessel in or adjacent to the illumination site.
- Planned surgery in first 28 days after treatment, except for planned surgical removal of the treated lesion.
- Planned dentist appointments in first 28 days after treatment.
- Anticancer therapy within the first 28 days after treatment.
- Therapy with drugs that induce light sensitivity (e.g. tetracyclines, sulfonamides, phenothiazines, sulfonylurea, hypoglycemic agents, thiazide diuretics, and griseofulvin) within the first 14 days after treatment.
- Co-existing ophthalmic disease likely to require slit-lamp examination within the first 28 days after treatment.
- History of hypersensitivity/anaphylactic reactions.
- Previous cumulative dose of Bleomycin received over 200 000 IE
- Known allergy or sensitivity to photosensitisers.
- Known allergy to Cremophor.
- Known allergy to bleomycin.
- Conditions contraindicated for bleomycin treatment (lung infection, impaired pulmonary function).
- Conditions that worsen when exposed to light (including porphyria).
- Conditions associated with a risk of poor protocol compliance.
- Pregnancy or breastfeeding.

4.5 Patient Withdrawal

Completion or trial termination for any reason will be fully documented in the “Trial Completion/withdrawal” CRF page.

Patients are free to withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason for withdrawal may include, but is not restricted to, withdrawal of consent, adverse event(s) or loss to follow-up. The reason(s) will be recorded in the CRF.

Patients withdrawing from the trial should be encouraged to go through the same final evaluations as patients completing the trial according to the protocol, with special focus on safety evaluations. The aim is to record data in the same way as for patients who complete the trial. Otherwise data will be recorded as consented by the patient and this consent will be recorded in the patient notes.

4.6 Trial Time Table

The anticipated time table for the trial is the following:

Anticipated start of recruitment: Q2 2009
Anticipated end of recruitment: Q1/2010
Anticipated end of follow up: Q3/2010

5. TREATMENT PROCEDURE

5.1 Pre-study (Day -14)

The pre-study evaluation will be performed to inform the patient about the study, and check eligibility for participation. No treatment or study related procedures will be initiated before the signed consent has been given. The pre-treatment evaluation should be done no more than 2 weeks before the baseline visit, or it can be combined with the baseline visit.

Pre-treatment evaluation will be performed according to the inclusion and exclusion criteria, including:

- Patient informed consent
- Inclusion and exclusion criteria
- Medical history and demographics
- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Performance status evaluation
- Concomitant medication
- Blood sampling for safety
- Pregnancy test (women of child-bearing potential)
- Lesion measurement (clinically) documented by ruler

5.2 Baseline Visit (Day 0)

Following successful completion of the pre-study evaluations, patients will continue to the baseline visit. It should take place within 14 days of the pre-study evaluation visit, or they can be combined. If the patient is still eligible for inclusion, the patient will be enrolled and receive treatment with Amphinex at this visit. The dose of Amphinex depends on which cohort the patient is enrolled in. The patient will be admitted to hospital prior to the administration of Amphinex and stay as an in-patient until 3 days after the bleomycin administration, Day 7. The in-patient stay will be prolonged as required if there are safety concerns after 7 days. The patient should not eat, drink or smoke for 6 hours prior to the Amphinex administration. After administration of Amphinex the patient must take precaution to protect the site of the injection of photosensitiser from light (e.g. with light protecting bandages). Appropriate protective clothing and eyewear will be supplied for the patients while they are in hospital and for them to take home if required. Precautions must also be taken to restrict light exposure of skin and eyes during the first days after administration as described in section 5.26 of the protocol. The patient will receive a light measure device to better control light exposure.

The following will be done at the baseline visit:

- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Performance status evaluation
- Document concomitant medication
- Blood sampling for safety, and pharmacokinetics
- Urine sampling for pharmacokinetics
- Lesion measurement clinically documented by photography and by ultrasound. If done previously, ultrasound should be no older than 4 weeks. In cases where the investigator

feels that ultrasound would not provide any significant additional information, only surface measurement of the lesion will be performed.
- Enrolment
- Pre-medication with steroids and antihistamines (H_1 + H_2 inhibitors)
- Fluorescence measurement (before administration of Amphinex), the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test (before administration of Amphinex), the procedure is described in section 5.24 of the protocol
- Skin photosensitivity score one hour after test illumination, documented by photography
- Amphinex administration
- Observation of the patient for at least two hours after Amphinex administration
- Reporting of adverse events (prior, during and after administration of Amphinex)

An assessment of all adverse events experienced since last visit and assignment of Common Terminology Criteria for Adverse Events (Refer to CTCAE v 4.0, Appendix F) grades to all those considered to be drug related will be done at this visit.

5.3 Visit 1 (Day 1)

Following successful completion of baseline visit, patients will continue to Visit 1. It should take place the day after the baseline visit.

The following will be done at Visit 1:

- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test, the procedure is described in section 5.24 of the protocol
- Skin photosensitivity score 24 hours after the baseline photosensitivity test, and 1 hour after the day 1 photosensitivity test, documented by photography

5.4 Visit 2 (Day 2)

Visit 2 will take place the day after visit 1.

The following will be done at Visit 2:

- Blood and urine sampling for pharmacokinetics
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin Photosensitivity score 24 hours after the test performed on day 1

5.5 Visit 3 (Day 3)

Visit 3 will take place the day after visit 2.

The following will be done at Visit 3:

- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test, the procedure is described in section 5.24 of the protocol

- Skin photosensitivity score 1 hour after the test illumination, documented by photography

5.6 Visit 4 (Day 4)

Visit 4 will take place the day after visit 3.

The following will be done at Visit 4:

- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Concomitant medication
- Blood and urine sampling for safety and pharmacokinetics
- Reporting of adverse events (since last treatment, including this treatment)
- Administration of bleomycin
- Observation of the patient for at least two hours after Bleomycin administration
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin Photosensitivity score 24 hours after the test performed on day 3
- Illumination with red light (laser 652 nm) 3 hours (+/- 30 minutes) after bleomycin administration, the procedure is described in section 5.22 of the protocol
- Pain assessment; immediately after illumination
- If required pain relief medication will be provided, details of the medication shall be given in the concomitant medication form

Maximal pain during the procedure will be recorded on a 10 centimetre visual analogue scale (VAS) immediately after the procedure. Pain will also be recorded 24 hours after the illumination and on day 4. The end-points of the VAS will be “no pain (0)” and “unbearable pain” (10).

The illumination can be paused if necessary. The reason should be recorded in the CRF.

An assessment of all adverse events experienced since last treatment and assignment of Common Terminology Criteria for adverse events (Refer to CTCAE v 4.0, Appendix F) grades to all those considered to be drug related will be done at this visit.

5.7 Visit 5 (Day 5)

Visit 5 will take place the day after visit 4.

The following will be done at Visit 5:

- Pain assessment; after 24 hours
- If required pain relief medication will be provided, details of the medication shall be given in the concomitant medication form

5.8 Visit 6 (Day 6)

- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test, the procedure is described in section 5.24 of the protocol
- Skin photosensitivity score 1 hour after test illumination, documented by photography

5.9 Visit 7 (Day 7)

Visit 7 will take place 7 days after the baseline visit.

The following will be done at Visit 7:

- Blood and urine sampling for pharmacokinetics
- Reporting of adverse events (since last treatment, including this visit)
- Photography of lesion
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity score, 24 hours after Day 6 test illumination, documented by photography
- Assessment prior to discharge

Patients should remain close to the hospital between day 7 and day 14 so that skin fluorescence and photosensitivity can be monitored. Patients who live far away may stay at the patient hostel after day 7.

5.10 Visit 8 (Day 9)

For the first subject in each new escalated dose group, the following tests are mandatory:
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test. The procedure is described in section 5.24 of the protocol
- Skin photosensitivity score 1 hour after test, documented by photography

For the subsequent subjects in each new escalated dose group the following tests may be carried out:
- Skin photosensitivity test required if skin reaction is seen in the patient on day 6, or at day 9 or later in a previous patient of the same dose group. The procedure is described in section 5.24 of the protocol.
- Fluorescence measurements will be performed if skin photosensitivity test is done, the procedure is described in section 5.23 of the protocol.

5.11 Visit 9 (Day 10)

- If skin sensitivity testing has been performed on Day 9, skin photosensitivity score should be performed 24 hours after Day 9 test illumination, documented by photography.

5.12 Visit 10 (Day 11)

For the first subject in each new escalated dose group, the following tests are mandatory:
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol.
- Skin photosensitivity test. The procedure is described in section 5.24 of the protocol.
- Skin photosensitivity score 1 hours after test, documented by photography.

For the subsequent subjects in each new escalated dose group the following tests may be carried out :

- Skin photosensitivity test required if skin reaction is seen in the patient on day 6, or at day 9 or later in a previous patient of the same dose group. The procedure is described in section 5.24 of the protocol.
- Fluorescence measurements will be performed if skin photosensitivity test is done, the procedure is described in section 5.23 of the protocol.

5.13 Visit 11 (Day 12)

- If skin photosensitivity testing has been performed on Day 11, skin photosensitivity score should be performed 24 hours after Day 11 test illumination, documented by photography.

5.14 Visit 12 (Day 14)

Visit 12 will take place 14 days after the baseline visit.

The following will be done at Visit 12:

- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Concomitant medication
- Blood sampling for safety and pharmacokinetics
- Urine sampling for pharmacokinetics
- Reporting of adverse events (since last treatment, including this visit)
- Photography of lesion
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol
- Skin photosensitivity test. The procedure is described in section 5.24 of the protocol
- Skin photosensitivity score at 1 hour after test, documented by photography

An assessment of all adverse events experienced since last treatment and assignment of CTCAE grades to all those considered to be drug related will be done at this follow-up visit.

5.15 Visit 13 (Day 15)

- Skin photosensitivity score 24 hours after Day 14 test illumination, documented by photography.

5.16 Visit 14 (Day 21)

- Skin photosensitivity test required if skin reaction is seen in the patient on day 14, or at day 21 or later in a previous patient of the same dose group. The procedure is described in section 5.24 of the protocol.
- Skin photosensitivity score 1 hour after test, documented by photography
- Fluorescence measurement will be performed if skin photosensitivity test is done. The procedure is described in section 5.23 of the protocol.

5.17 Visit 15 (Day 22)

- Skin photosensitivity score 24 hours after Day 21 test illumination (if applicable), documented by photography.

5.18 Visit 16 (Day 28)

Visit 16 will take place 28 days (+/- 1 day) after the baseline visit.

The following will be done at Visit 16:

- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Performance status evaluation
- Concomitant medication
- Blood sampling for safety and pharmacokinetics
- Urine sampling for pharmacokinetics
- Reporting of adverse events (since last treatment, including this visit)
- Lesion response evaluation according to RECIST (Appendix E) documented by photography and ultrasound
- Fluorescence measurement, the procedure is described in section 5.23 of the protocol.
- Skin photosensitivity test required if skin reaction is seen in the patient on day 14, or at day 21 or later in a previous patient of the same dose group. The procedure is described in section 5.24 of the protocol.
- Skin photosensitivity score 1 hour after test, documented by photography.

An assessment of all adverse events experienced since last treatment and assignment of CTCAE grades to all those considered to be drug related will be done at this follow-up visit.

5.19 Visit 17 (Day 29)

- Skin photosensitivity score 24 hours after Day 28 test illumination (if applicable), documented by photography.

5.20 Visit 18 (3 months)

Approximately 3 months (+/-1 week) after the baseline visit, the last follow-up visit will be performed:

- Vital signs (blood pressure; average of 2 measurements, heart rate)
- Concomitant medication
- Blood sampling for safety and pharmacokinetics
- Urine sampling for pharmacokinetics
- Reporting of adverse events (since last treatment, including this visit)
- Performance status evaluation
- Lesion response evaluation according to RECIST (Appendix E), documented by photography and ultrasound or surface measurement

- Fluorescence measurement, the procedure is described in section 5.23 of the protocol.
- Skin photosensitivity test required if skin reaction is seen in the patient on day 14, or at day 21 or later in a previous patient of the same dose group. The procedure is described in section 5.24 of the protocol.
- Skin photosensitivity score 1 hour after test, documented by photography.

An assessment of all adverse events experienced since treatment visit and assignment of CTCAE grades to all those considered to be drug related will be done at this follow-up visit.

5.21 Visit 19 (1 day after the 3 month visit)

- Skin photosensitivity score 24 hours after the 3 months test illumination (if applicable), documented by photography.

5.22 Illumination of the tumour site

Illumination is started after the fluorescence measurements at day 4. For additional fields, the illumination procedure must be repeated. There is a time window of **3 hours (+/- 30 minutes)** between bleomycin administration and illumination. A physician must be present during the illumination. The patient is installed comfortably lying down. The patient and all persons participating in the treatment session should wear protective goggles during the illumination.

1. Cover the skin around the lesion that will be illuminated with aluminum tape or dark, closely woven clothing, so that this area does not receive any light.

2. Connect the light distributor fiber (Medlight FD) to the laser (Ceralas PDT 652). Switch the laser on using the main power switch and the key switch, and follow the internal calibration procedure as instructed on the display. **Ensure that the fiber tip is pulled 1–2 cm back from the bottom of the calibration port** during the calibration. (The system can be damaged if the fiber tip is touching the bottom of the calibration port during light output).

3. Adjust the illumination time to 600 seconds.

4. Turn the aiming light on by pressing *AIMING ON/OFF*. Position the fiber tip normally to the target surface at a distance of 5 to 7.5 cm. The distance, or the corresponding beam diameter, should be fixed at one of the values suggested in the table below. **Adjust the laser output power** according to the table. This will ensure that the target is exposed to an irradiance of 100 mW/cm^2.

distance	spot diameter	Power
5.0 cm	3.3 cm	0.85
5.5 cm	3.6 cm	1.03
6.0 cm	4.0 cm	1.23
6.5 cm	4.3 cm	1.44
7.0 cm	4.6 cm	1.68
7.5 cm	5.0 cm	1.92

5. Ensure that the patient and all personnel are wearing safety goggles. Enable the laser by pressing *ENABLE/STANDBY*. The illumination can then be started using the footswitch. The display will show the time remaining. The illumination can be interrupted and restarted at any time by pressing the footswitch.

6. ~~Ensure that the patient and all personnel are wearing safety goggles. Enable the laser by pressing *ENABLE/STANDBY*. The illumination can then be started using the footswitch. The display will show the time remaining. The illumination can be interrupted and restarted at any time by pressing the footswitch.~~

7. When the illumination is completed, the output power should be measured. Press *RESET TIME*, press *ENABLE/STANDBY*, and insert the fiber into the calibration port. Use the footswitch to start and stop the laser while the fiber is inside the calibration port. The output power is showed on the display, and should be within ±20% of the value selected with the power knob. Press *ENABLE/STANDBY* to disable the laser.

The max power showed on the display during calibration, the distance/diameter, the selected power, and the power measured after illumination should be written into the CRF. **If the illumination has been paused and restarted**, please make sure to tick the appropriate box on the CRF. Conduct the assessment of pain immediately after the procedure.

To switch off the laser, press *POWER OFF* three times. When the message "LASER READY FOR SWITCH OFF" is displayed the laser can be switched off using the main power switch.

5.23 Fluorescence measurements

Prolonged skin photosensitivity is a non-negligible side effect of most photosensitisers used systemically today for PDT. Phototoxic reactions following light exposure of photosensitive skin include erythema, oedema and occasionally cutaneous blistering of the hands and face and discoloration. These side effects are related to the skin's content of Amphinex, which can be assessed by non-invasive fluorescence measurements. Such measurements can then be compared with a skin photosensitivity test in order to establish how fluorescence from the skin is related to phototoxic reactions induced by light.

Amphinex fluorescence intensity from the skin surface will be measured using a Biolitec JET1 PDT fluorometer. The probe exposes a target area to blue excitation light, and collects the fluorescence light emitted from the target area. The fluorometer quantifies the amount of fluorescence light around the Amphinex fluorescence maximum around 670 nm. Each measurement takes less than a second and does not cause any pain or discomfort.

At baseline there will be fluorescence measurements at two sites at the patient's arm, in areas that are not used for photosensitivity tests or Amphinex infusion. The background fluorescence measured at baseline will be subtracted from each fluorescence measurement performed at the following time points. Two fluorescence measurements will be performed at each site for each time point.

Measurements are performed at the time points specified in the study flow chart (Appendix B). The fluorescence measurements performed at day 0 should be done before Amphinex

administration and the day 4 measurements must be done prior to the illumination that will be done the same day. At each time point the fluorescence is measured at two sites of normal skin at the patients arm. During the study the measurement sites are marked carefully, without interfering with the target area, to ensure that the probe is placed exactly on the same spot for each measurement. Hold the probe gently towards the skin during the measurement, as pressure may affect the measurement.

5.24 Skin photosensitivity measurements

Systematic skin photosensitivity tests will be carried out using a white light source with an emission spectrum that, relatively to the luminance and within +/- 50%, excites Amphinex with the same efficiency as sunlight. The luminance will be 500 lux, which is comparable to bright indoor light, and 100.000 lux, which is comparable to direct sunlight. The phototoxic reaction will be scored at specific time points following the light exposure (see the study flowchart). This information will be used to predict the degree of photosensitivity of the skin.

Measurements are performed at the time points specified in the study flow chart (Appendix B). Separate 0,8 cm^2 spots on the arm of the patient, in areas that are not used for fluorescence measurements or Amphinex infusion, will be exposed at day 0 (before Amphinex administration), 1, 3 and 6. Tests will also be performed at day 9, 14, 21 and 28 if there is still photosensitivity at the previous visit. No single spot will be used for more than one exposure. To avoid severe phototoxic reactions each test will be discontinued if the patient experiences distinct pain related to the light exposure. At day 0 separate sites will be exposed to 500 lux for 5 minutes, 100 000 lux for 30 seconds, and 100 000 lux for 5 minutes. At day 1 different sites will be exposed to 500 lux for 5 minutes and if no reaction within 1 hour, then for 100 000 lux for 30 seconds. At day 3, previous tests can be omitted if no reactions are seen from the previous test, and 100 000 lux for 5 minutes can be tested. For tests at remaining days, see Table 1.

Procedure at each time point:

- Start with the lowest light dose. **Set the correct luminance** (500 or 100.000 lux) and exposure time (30 seconds or 5 minutes).
- Position the lamp with the 1 cm diameter illumination aperture adjacent to the skin and start the exposure. **Stop the exposure and discontinue the procedure if the patient experiences distinct pain** related to the light exposure.
- If no immediate skin reactions or pain related to the light exposure have been experienced: Reposition the lamp to a new spot, and repeat the procedure using the next light dose specified for the current time point. There should be a **1 hour interval before the 100.000 lux – 5 minute exposure**. This interval is omitted if a previous 100.000 lux – 5 minute exposure for the same patient did not cause a significant skin reaction.

The spots will be marked, scored, and photographed 1 and 24 hours after illumination. The photographs should be of high quality, and result in paper copies. Take close-up photos of each spot, including the label identifying patient number, spot number and date of visit.

Table 1. Flowchart skin photosensitivity test
Measurements are performed at the time points specified in the study flow chart (Appendix B).

Skin photo-sensitivity test	**Day 0 (prior to Amp)**	**Day 1**	**Day 3, 6, 9, 11, 14, 21**	**Day 28**	**Day 90 (3 months)**
Luminance (lux) & Exposure time	1 2 3	1 2 †	1 § 2 § 3	2 § 3	3

1= 500 lux, 5 min
2= 100 000 lux, 30 sec
3= 100 000 lux, 5 min

† Only if the 500 lux, 5 min exposure did not cause pain or significant phototoxic reactions within a 1 hour interval
§ This exposure will be omitted if the previous exposures at the same level did not cause significant phototoxic reaction

The Amphinex fluorescence measurements may suggest major changes in the skin photosensitivity since the last photosensitivity test, indicating a change in the precautions necessary to prevent phototoxic reactions. In such cases, optional photosensitivity tests may be performed at other time points than those mentioned above.

5.25 Pharmacokinetics

Plasma samples for pharmacokinetic (PK) evaluation will be collected from patients and the presence of Amphinex and/or other unidentified metabolites will be assessed using a validated analytical method. Blood samples for PK evaluation will be collected during day 0 (before and after Amphinex administration) 2, 4, 7, 14 and 28 for all patients. If a patient discontinues before the day 28 visit an effort should be made to obtain a blood sample for PK evaluation at the time of discontinuation. For the purpose of collecting adequate population PK data, the exact time that a blood sample is drawn should be recorded. The patient should not eat, drink or smoke for approximately 6 hours prior to the Amphinex administration and the PK sample taken on day 0.

Blood samples will be collected before, approximately 30 minutes after, and 4 hours after dosing at day 0. Blood will be collected in test tubes containing lithium heparin as an anticoagulant, and divided into two aliquots. Additional analyses may be conducted for further metabolite identification or other determinations, but the blood volume will not increase.

Urine samples will be collected at the same time points as the PK blood samples. Urine samples will be measured for the presence of Amphinex and/or other unidentified metabolites.

Standard non-compartmental procedures will be used to evaluate the pharmacokinetics behavior of Amphinex.

Dose linearity will also be assessed by comparing maximum concentrations and area under the curve measurements across the dose range tested, when data are available.

5.26 Precautions for use

It is expected that all patients that receive Amphinex will become temporarily photosensitive. Precautions must be taken to protect the area of the photosensitiser infusion from light. The infusion site must be protected by a dressing with a black, non-transparent layer. Precautions must be taken to avoid exposure of skin and eyes to direct sunlight or bright indoor light during the first days after injection. Skin photosensitivity reactions are caused by visible light; therefore ultraviolet sunscreens provide no protection. It is important that patients are re-introduced to normal light gradually.

Clinicians must counsel patients to observe the following precautions:

Time after Amphinex Injection	**Precautions to prevent skin sensitivity reactions**
Day 1 (0-24 hours)	Stay indoors in a darkened room. Keep the curtains drawn and use light bulbs of 60W or less. **Avoid direct exposure of eyes from light source. Avoid exposure to direct sunlight.**
Following days	**Avoid direct sunlight coming through the window** or direct light from household appliances such as reading lamps. The patient may watch television. Gradually return to normal indoor lighting by increasing the light by one 60 W light bulb every day. The patient can go outdoors after dusk. If it is absolutely necessary to go outdoors during the hours of daylight, the patient must be careful to **cover up all of the skin including face and hands and wear dark glasses**. The type of clothes the patient must wear are: • Wide-brimmed hat: for head, neck, nose and ears • Scarf: for head and neck • Sunglasses with side panels: for eyes and skin around eyes • Long sleeved top: for upper body/arms • Long trousers: for lower body/legs • Gloves: for hands, wrist and fingers • Socks: for feet and ankles

	• Closed shoes: for feet Do not wear very thin clothing, because it cannot protect from strong light. Wear dark, closely woven clothing. If the patient is exposed to light by mistake, the patient may get a prickly or burning feeling on the skin. The patient must get out of the light **immediately**. The patient eyes may be very sensitive to bright lights during this week and should wear dark glasses. When the patients skin sensitivity test doesn't show any phototoxic reactions like burning or swelling reactions from exposure to 100.000 lux for 30 seconds, the patient can go outside during daylight hours. The patient should stay in shaded areas or go out when it's cloudy. The exposure should not exceed more than 5 000 lux measured on the patient's light measure device. Continue to wear sun glasses and dark, closely woven clothing. The patient should start with 15 minutes outdoors. Wait 24 hours to see if there is any redness. If there is no redness, the patient can gradually increase the time outdoors. If there is redness, the patient should try again with the same exposure level at the next skin sensitivity test. When the patients skin sensitivity test doesn't show any phototoxic reactions like burning or swelling reactions from exposure to 100.000 lux for 5 minutes, direct sunlight should be tested carefully by exposing the back of the hand to the sun for 5 minutes. Continue to wear sun glasses and dark, closely woven clothing. Wait 24 hours to see if there is any redness. If there is redness, the patient should avoid direct sunlight for another 24 hours, and continue to wear sun glasses, dark, closely woven clothing and avoid direct sunlight or strong indoor lighting. The patient can then repeat the test. If there is no redness, the patient can gradually increase the exposure to sunlight day by day. Do not stay in direct sunlight for more than 15 minutes the first time. The patient can increase the exposure by another 15 minutes each day i.e. second day 30 minutes, third day 45 minutes, fourth day 60 minutes and so on. If at any time the patient notice a prickly or burning feeling or see skin reddening after exposure to sun, wait until this disappears before exposing skin to light for this length of time again For 30 days following Amphinex treatment, avoid eye tests that use bright lights. For 3 months following Amphinex treatment, avoid UV tanning beds and do not sunbath.

Not planned or emergency surgical procedures, where Amphinex was administred in the previous 30 days, must only be done if absolutely necessary and if the potential benefits for the patient is greater than the risk. One must make any precausion to avoid direct illumination of the patient with the operating room lights and surgical lamps, including the

surgeons headlamp, by covering them with yellow filter during these procedures. All incisions should be shielded from light [27]. It's recommended that Clinidrape paper, 4 layers, are taped as close to the skin edges as possible, secured with skin staples of the type Tyco Autosutur APPOSE UCL, every 5 mm of the length.

5.27 Patient Compliance

Treatment consists of one treatment of one dose of Amphinex and bleomycin and will be administered in the hospital by suitably qualified staff. The patient must follow precautions regarding skin sensitivity reactions as stated in section 5.26. Appropriate sunglasses and additional suitable clothing (according to section 5.26) will be provided by the sponsor, whilst the patients are in hospital and also for them to take home, as required. Patients who fail to comply with the safety precautions, may be considered protocol violators.

6. ASSESSMENT OF EFFICACY

6.1 Efficacy

While efficacy is not a primary objective of this study, lesion responses will be followed and evaluated according to RECIST (see Appendix E).

Baseline visit (Day 0):

At the baseline visit each patient will be assessed with the following procedures:

- Performance status evaluation
- Lesion measurement and documentation by ultrasound

Study Visit 10, 14, and 16 (Day 14, 28 and 3 months):

All patients will be seen at day 14, 28 and 3 months after treatment with the study drug. At this time, performance status evaluation, lesion response evaluation at day 28 and 3 months according to RECIST (Appendix E).

6.2 Photographs

Photographs will be taken of the target lesion areas included in the study at baseline before treatment and at the follow-up visit at day 7, 14, 28 and at 3 months. These photographs should be of high quality and result in paper copies. Next to the lesion a ruler with a millimetre scale will be attached to the skin. This ruler will also present the identification of the subject, i.e. subject number, date and field number. PCI Biotech AS will supply these adhesive rulers.

The photographic procedure will be as follows:

1) Baseline: Take an overview picture of the area to be treated. Take close-up photos of each field, including the ruler available as an adhesive tape (identifying patient number and date of visit). The photos taken should ensure that the investigator will be able to locate the lesions at the response assessment visit. A transparent grid might be included in some photos to guide the positioning of the grid at the response assessment visit.

2) Study Visit 7, 10, 14 and 16 (Day 7, 14, 28 and 3 month): Use the previous photos treated area, to aid in making identical photos with regards to light and distance. Repeat the procedure as described above for baseline photos.

3) As soon as the prints are developed and returned, put them (with patient identification) in plastic folders.

7. SAFETY

The investigators are responsible for monitoring the safety of patients who have entered this study and for reporting to the sponsor if serious adverse events (SAE) occurred.

The investigator is responsible for appropriate medical care of patients during the study.

The investigator remains responsible to follow, through an appropriate health care option, adverse events that are serious or that caused the patient to discontinue before completing the study. In case of an adverse event, the patient must be followed until the event resolves or clinically required. Frequency of follow-up is left to the discretion of the investigator.

If the patient has a pre-planned procedure (e.g. hip replacement surgery) that will take place during the study period, this must be recorded at baseline in the CRF and should NOT be reported as a SAE.

After administration of Amphinex the patient must take precaution to protect the site of the injection of photosensitiser from light (e.g. with light protecting bandages). Precautions must also be taken to restrict light exposure of skin and eyes during the first days after administration as described in section 5.26 of the protocol. The patient will receive a light measure device to better control light exposure. Protective eyewear and appropriate protective clothing will be provided by the sponsor as required

The Investigator is responsible for ensuring that there are procedures and expertise available to cope with emergencies during the trial should they occur. If any intolerable side effects occur, the treatment will stop and the patient will be withdrawn from the study.

7.1 Serious Adverse Events

7.1.2 Definition of a Serious Adverse Event

A SAE is any untoward medical occurrence that at any dose:

- results in death,
- is life threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect.
- is another medically important condition

7.1.3 Reporting of Serious Adverse Events

Patients should be closely followed for adverse events while on study drug and for 30 days after the last dose of study drug in order to detect delayed toxicity. Whether or not the adverse events are considered related to the study drugs, they must be reported. After this period, the investigator should report only serious adverse events which are felt to be causally related to study drug therapy or protocol procedure.

Serious adverse events occurring more than 30 days after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure.

Pregnancies occurring within the 3-month period after the last treatment, and coming to the attention of the investigator, should be followed until the baby has been delivered, in order to document any congenital anomalies or birth defects, should they occur.

All serious adverse events (SAE) must be reported to LINK Medical Research AS as follows:

1. Immediately (within 24 hours of discovery of the event) report the event to LINK Medical Research AS by telephone or fax.
2. Complete the SAE report form and fax or e:mail it to LINK Medical Research AS within three (3) working days of the discovery of the event.
3. Follow up the SAE until resolved or as clinically required, all follow-up evaluations must be reported to LINK Medical Research AS.
4. Record the SAE in the patient case report forms (CRF) provided.
5. Document the SAE in the hospital records.

LINK Medical Research AS must be notified by telephone when a document has been sent by fax. If limited information on the event is initially available, follow-up reports will be required.

LINK Medical Research AS	telephone:	+47 46 42 69 29
	telefax:	+47 22 58 94 55
	e:mail	pv@linkmedical.no

The investigator and LINK Medical Research AS or its designee is responsible for reporting SAE's to Ethics Committee/IRB and regulatory authorities according to local regulations.

7.2 Adverse Event

7.2.1 Definition Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment, reported during or after having received the investigational drug/procedure. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

7.2.1 Reporting of Adverse Event

All adverse events will be reported in the patient case report forms (CRF) provided, but also in the patient's hospital notes. Local phototoxicity and outcome descriptors (e.g. hypopigmentation, hyperpigmentation, scarring, atrophy, induration and tissue defects) will also be reported as adverse events by the investigator. All adverse events will be followed up until resolved or as clinically required (i.e. post partum in case of pregnancies).

7.2.3 Assessment of Adverse Event

A baseline recording of any symptoms of illness will be performed before administration of the investigational product. Only symptoms that increase in severity after study drug administration or new symptoms of illness will be recorded as adverse events in the CRF.

Adverse events will be assessed from the patients entering the study until 30 days after last dose of study drug. Adverse events may be reported spontaneously by the patient or elicited through open (non-leading) questioning during each visit and at the end of the trial. As far as possible, all adverse events must be described by their duration (start and stop date), severity (mild, moderate or severe; see **Section 7.2.4**), relationship to treatment (yes, uncertain, no; see **Section 7.2.5**) and according to the need of other specific therapy. Localisation of adverse events will be recorded as "treatment site" or "non-treatment site", see **Section 7.2.6**. The onset of adverse events will be classified relative to the stage of treatment as described in **Section 7.2.7**. All information will be recorded on the "Adverse event" pages in the CRF together with the patient hospital journal.

7.2.4 Severity of Adverse Event

Adverse events as:

Mild the adverse event is transient and easily tolerated.

Moderate the adverse event causes the patient discomfort and interrupts the patient's usual activities.

Severe the adverse event causes considerable interference with the patient's usual activities, and may be incapacitating or life-threatening.

CTCAE grading will be assigned to all adverse events considered to be drug related.

7.2.5 Relationship of Adverse Event to Investigational Drug

The Investigator's opinion of the relationship of the adverse event(s) to the investigational drug will be assessed as *Not related, Unlikely*, *Possible* or *Probable*. For these purposes, the following definitions will be used:

Not related A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship unlikely, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by

concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probable: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other chemicals, and which follows a clinically reasonable response on withdrawal.

7.2.6 Localisation of Adverse Events

The investigator should report localisation for all adverse events.

Treatment site: Occurring in any of the treated fields.

Non-treatment site: Occurring outside the treated fields.

7.2.7 Onset of Adverse Events

The investigator will classify the onset of each adverse event relative to the following stages of treatment:

During or after Amphinex infusion, before bleomycin infusion.

After Amphinex and bleomycin infusion and before illumination.

During or immediately after illumination.

After treatment.

7.3 Clinical laboratory tests

On the pre-study visit, no more than 2 weeks before enrolling into the study, each patient will be assessed with the following tests:

- **Serum Chemistry:** sodium, potassium, bilirubin, alkaline phosphatase (ALP), alanine aminotransaminase (ALT), urea, creatinine, phosphorus, calcium, glucose, albumin..

- **Hematology**: Hb, RBC, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

- **Urine pregnancy test** must be performed for women of child-bearing potential. Initial screening results will be used to determine if the patient is eligible for protocol enrollment.

At day 0, 4, 14 and 28 after treatment with the study drug the following test will be done:

- **Serum Chemistry**: sodium, potassium, bilirubin, alkaline phosphatase (ALP), alanine aminotransaminase (ALT), urea, creatinine, phosphorus, calcium, glucose, albumin.

- **Hematology:** Hb, RBC, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

The local laboratory at the local site will be used. The investigator must document the review of each laboratory report by signing or initialling and dating each report.

Upon discontinuation from the study less than 30 days after last study drug dose, patients will be assessed with the following tests, unless these tests have been already conducted within 3 days of discontinuation:

- **Serum Chemistry:** sodium, potassium, bilirubin, alkaline phosphatase (ALP), alanine aminotransaminase (ALT), urea, creatinine, phosphorus, calcium, glucose, albumin.

- **Hematology**: Hb, RBC, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

7.4 Composite score for skin photosensitivity reaction

A composite score for photosensitivity reaction will be calculated for each time-point. This score will consist of the sum of the scores for erythema and oedema. Each of these symptoms will be scored on a scale from 0–3 (none, mild, moderate or severe) and will be recorded in the CRF for all time points. The composite score will be plotted over time, in order to generate time-intensity curves for the photosensitivity reaction.

Symptoms that are graded severe will be treated at the discretion of the investigator and followed-up until resolved. Every patient will be evaluated 1 and 24 hours after every exposure. Based on these evaluations, the exposures will be adjusted if thought necessary by the responsible investigator.

7.5 Pain

Maximal pain during the procedure will be recorded immediately after the procedure on a 10 centimetre visual analogue scale (VAS). Pain will also be recorded 24 hours after the illumination and on day 4. The end-points of the VAS will be “no pain” and “unbearable pain”.

8. STATISTICAL EVALUATION

8.1 Justification of Sample Size

Potentially, four dose levels of approximately 3 to 6 patients will be enrolled in the study. Further dose levels may be enrolled depending on the actual number of dose levels tested prior to reaching the maximum tolerated dose (MTD). In addition, at the dose level selected for subsequent efficacy trial, minimum 6 additional patients will be treated.

Any patient, who is withdrawn from the study before completing the 28 day follow-up visit, without experiencing dose-limiting toxicity (DLT) prior to withdrawal, will be deemed non-evaluable for determining dose escalation and the MTD. Any non-evaluable patients will be replaced to ensure that 3 to 6 patients complete 28 day follow-up visit at each dose level, unless accrual to that cohort has stopped due to DLT.

8.2 Definition of Study Population

8.2.1 Safety Population

All patients who receive Amphinex and bleomycin will be included in the All Patients Treated (APT) population.

8.2.2 Per-Protocol Population

In this dose-escalating study the focus is on safety issues. A per-protocol analysis population that comprises all patients who followed the protocol is applicable only as supporting analysis population for specific analysis such as fluorescence measurements; photosensitivity, pain, laboratory findings, pigmentation changes and lesion response evaluation according to RECIST (see Appendix E). It may be reasonable to exclude patients who violated the protocol in a way that their measurements would lead to inappropriate conclusions. Details will be specified in the Statistical Analysis Plan (SAP).

8.3 Statistical Analysis

Statistics will be performed by a qualified biostatistician. Tabulation of summary statistics and data analysis will be performed using SAS software. The results will be presented in tables with number of patients, mean, standard deviation, minimum and maximum for continuous data and with frequencies and percentages of patients for categorical data.

8.3.1 Disposition of Subjects

A detailed description of patient disposition will be provided. It will include the following:

- A definition of patient qualification.
- A summary of data on overall qualification status of all patients.
- An account of all identified protocol violations.
- A summary of data on patient discontinuation and reasons for discontinuation.

All patients entered in the study will be accounted for in the summation.

8.3.2 Demography and baseline characteristics

Patient characteristics such as sex, age, race, and Fitzpatrick score will be described using summary statistics. Medical history and information about the underlying disease as well as concomitant medication will be summarised. Lesion characterisation will be given. Tables will be presented for APT and PP stratified by dose level.

8.3.3 Efficacy

A formal efficacy analysis is not appropriate for this trial. The response data will be documented by descriptive summary tables. No statistical comparison of dose levels will be done. Fluorescence measurements over time and lesion response evaluation according to RECIST (see Appendix E) will be presented for APT and PP stratified by dose level.

8.3.4 Safety

All patients who receive one dose of Amphinex will be evaluated for safety and toxicity. Safety analyses will include the following:

- Summaries of the adverse event rates and laboratory changes from baseline stratified by dose level.
- Listings and frequency tables categorizing laboratory and non-laboratory adverse events by maximum CTCAE toxicity grade and relationship to study drug.
- Pain measurement, fluorescence measurement, skin photosensitivity measurement

8.4 Handling of Missing and Spurious Data

Individual subject data will only be excluded from the evaluation when a protocol violation is considered to weaken any of the scientific aspects of the study. Missing data will generally not be substituted by estimated values.

8.5 Interim Analysis

Since this is a dose-escalation study, data will be evaluated by the involved investigators and sponsor continually during the conduct of the trial. No formal interim analysis is planned for this study.

8.6 Pharmacokinetic Analyses

The plasma concentration versus time data, together with information on dosing and patient characteristics will be pooled and analyzed using a population PK analysis approach.

9. DATA MANAGEMENT

9.1 Patient Data Protection

Patient number, year of birth, race and sex will identify the patients in the CRF's.
The investigator is responsible for keeping a list of all randomized patients including patient numbers, full names and date of birth. In addition, the investigator will prepare a list of patients who were screened for participation of the trial but were not randomized and the reason for non-eligibility.

The patients will be informed in writing that the results will be stored and analyzed in a computer according to national laws, as applicable, and that patient confidentiality will be maintained.

The patients will also be informed in writing about the need for source data verification (SDV), audits and inspections. The audit/inspection and SDV will be performed by at least one of the following parties; authorized representatives of PCI Biotech AS, authorized monitors, hospital IRB's/EC's or regulatory authorities. In these cases the relevant part of the patient's notes will be required and reviewed.

9.2 Data Handling

The investigator or his/her designee will document all data obtained during the study using the electronic data capture system provided by PCI Biotech AS. This also applies to data for those patients who, after having consented to participate, underwent baseline examinations required for inclusion into the trial, but who were not included in the study.

In the process of ensuring data completeness and accuracy, a 100% Source Data Verification (SDV) will be performed. The investigator will complete and maintain source documents for each subject participating in the study. Source data is the first place the data is recorded, regardless of where this is. AE's and SAE's together with visit dates and information about the disposition for each patient should be recorded in the patient notes (see also Section 3.12).

For all patients, PCI Biotech AS or its designee will validate the completed CRF's. The Investigator will retain a copy of the printed CRF. If data management detects CRF's with missing or inconsistent data not catered for, queries will be sent into the system for correction by the Investigator. The Investigator will also receive data query, which might be generated during the computerized data validation process.

Source data, source documents, CRF's, protocol and amendments, drug accountability forms, correspondence, patient identification list, informed consent forms, and other essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained consistent with regulations under CFR 312.62 Part C, April 1, 1995 and ICH guidelines (GCP).

PCI Biotech AS or its designee will be responsible for data processing and data control. Data management will be carried out as described in PCI Biotech AS or its designee Standard Operating Procedure (SOP's) for clinical studies. Patient data will be entered continuously.

All original documents and CRF's will be retained in the archives of PCI Biotech AS as long as the product under investigation remains available for human use. The final report will be retained in the archives of PCI Biotech AS for five years after the product is no longer authorized.

10. ADMINISTRATIVE PROCEDURES

10.1 Investigator Information

The investigational site will receive an "Investigator Site File" with information specifically related to the trial.

10.2 Curriculum Vitae

All Investigators and study nurses participating in the study, including those who will sign the CRF's will supply PCI Biotech AS or its designee with curricula vitae (CVs).

10.3 Trial Amendment and Discontinuation

Any changes to the protocol or discontinuation of the trial require a written protocol amendment or statement, respectively. The investigators, appropriate EC (in UK an EC approved by UK Ethics Committee Authority) in some cases and PCI Biotech AS must approve the protocol amendment or statement.

National authorities and appropriate EC will be notified about all protocol amendments or discontinuation of the trial. If the protocol amendment results in major changes, affecting patients' safety, the objective(s) or the scientific quality of the study, it must be approved by the hospital/appropriate EC, as well as by the national regulatory authorities.

PCI Biotech AS will have the right to terminate the trial at any time in case of serious adverse events or if special circumstances concerning the trial substance or the company itself should occur, making further patient treatment impossible. PCI Biotech AS will inform the investigators about the reasons for trial termination.

10.4 Insurance and Liability

PCI Biotech will provide a letter if requested, outlining the terms and conditions of indemnification.

10.5 Ethics Committee and/or Institutional Review Board

The trial will be conducted in accordance with the Declaration of Helsinki 1964 including the most recent amendment (Edinburgh, Scotland, October 2000).

The trial protocol, including the patient information and informed consent to be used, must be approved by the appropriate EC. Written approval must be obtained before enrolment of any patients into the trial. It is the responsibility of the investigator to supply sponsor with the Letter of Approval defining the version of each document approved.

The principal investigator will ensure that this study is conducted in full conformance with the Edinburgh, Scotland, (2000) amendment to the Declaration of Helsinki 1964 (**Appendix C),** 21 CFR part 50, and with national laws and regulations for clinical research.

The investigator is responsible for informing the ethics committees and regulatory authorities of any serious adverse events and/or major amendments to the protocol as per national

requirements. The investigator should file all correspondence and a copy should be sent to CRO.

10.6 Patient Informed Consent

The investigator is responsible for giving the patient complete verbal and written information about the nature, purpose, possible risks and benefits of the trial. Trial patients must also be notified that they are free to withdraw from the trial at any time. The subjects should have reasonable time to read and digest the information before signing. The investigator is responsible for obtaining signed IRB approved informed consent from all patients before performing any trial related procedures.

A copy of the Patient Information and of the Patient Informed Consent Form will be given to the patients. The signed consent form will be kept by the investigator, in the Investigator Study File.

10.7 Regulatory Affairs

A notification will be submitted to national authorities before commencement of the trial, as applicable according to local regulations. Notifications and reports will be filed according to ICH E6: Good Clinical Practice: Consolidated guideline, CPMP/ICH/135/95, and national guidelines.

10.8 Trial Monitoring

Prior to the start of the study, the monitor will review the protocol, CRF's and other study documents and procedures with the investigator and their staff. The investigator will be visited on a regular basis by the monitor, who will check trial procedures, including safety assessments, drug handling, data recording and source data verification (SDV). The monitor will be allowed to review relevant clinical records to confirm that required protocol procedures are being followed and check consistency between patient record and CRF. Incorrect or missing entries into the CRF's will be addressed as data queries and must be corrected immediately. Trial monitoring will not jeopardize patient confidentiality.

10.9 Trial Audits and Inspections

During or after the trial has been completed PCI Biotech AS representatives may wish to carry out an audit. Regulatory bodies may also inspect the study. These representatives will have the same access to trial data and patient source data as the monitor. If a regulatory authority contacts the investigator with a request for an inspection, the investigator must inform the monitor immediately.

10.10 Financing

A separate financial agreement (Clinical Trial Agreement) will be signed between PCI Biotech AS and the investigator and/or the institution involved.

11. CONFIDENTIALITY AND COMMUNICATION OF RESULTS

All information concerning PCI Biotech AS research and product development is considered confidential and will remain the sole property of PCI Biotech AS. This includes patent applications, manufacturing processes not previously published and Investigator Brochures.

11.1 Statistical and Clinical Reports

Patient listings including safety data, efficacy and biopsy findings will be prepared shortly after receiving all patient data. In all listings patients will be identified by their patient number, initials and year of birth only.

PCI Biotech AS will also draft and finalize the research (integrated clinical and statistical) report. The integrated report will be added to the PCI Biotech AS data file and may be used for regulatory purposes and/or in company publications.

If the trial is terminated prematurely for any reason, an abbreviated report will be prepared.

11.2 Publication

All data from the study is free for publication. However, if publication of the results may endanger the possibility of obtaining adequate patent protection for new principles, compounds or formulations, PCI Biotech AS has the right to decided when the results are free to be published.

The statistical/clinical trial report may form the basis for a manuscript intended for publication in a scientific journal at a suitable time agreed by the investigator and PCI Biotech AS. Before this agreed time, no data from the trial will be published, presented or communicated, except to regulatory authorities and ethics committees. Both the investigator and PCI Biotech AS will be given 30 days to review and comment on any manuscript/abstract or other means intended for publication or presentation of the data.

The published international guidelines for authorship (International Committee of Medical Journal Editors, 1997) will be adhered to; i.e. ‘All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.’

Authorship credit will therefore be based only on substantial contributions to

1 Conception and design, or analysis and interpretation of data
2 Drafting the article or revising it critically for important intellectual content
3 The final approval of the version to be published.

It is the intention that the co-ordinating investigator will be first author; however the final decision on the order of authorship will be decided before study start.

11.3 Regulatory Use of Data

By signing the protocol, the investigators agree that the results of this study may be used for submission to national and/or international registration and supervising authorities. The

authorities will be notified of the investigators name, address, qualifications and extent of involvement.

REFERENCES

1. NCI home page, August 2006
2. A.P. Castano, P. Mroz, M.R.Hamblin, Photodynamic therapy and anti-tumor immunity, Nature Rev. 6 (2006) 535-545.
3. M. Korbelik, G. Krosl, J. Krosl, GJ Dougherty, The role of host lymphoid populations in the response of mouse EMT6 tumor to photodynamic therapy. Cancer Res. 56(1996) 5647-52.
4. M. Korbelik, GJ.Dougherty, Photodynamic therapy-mediated immune response against subcutaneous mouse tumors, Cancer Res. 59 (1999) 1941-6.
5. SO. Gollnick, L. Vaughan, BW. Henderson, Generation of effective antitumor vaccines using photodynamic therapy, Cancer Res. 62 (2002) 1604-8.
6. AP. Castano, Q. Liu, MR. Hamblin, A green fluorescent protein-expressing murine tumour but not its wild-type counterpart is cured by photodynamic therapy. Br J Cancer, 94 (2006) 391-7.
7. M .Korbelik, J. Sun, Photodynamic therapy-generated vaccine for cancer therapy. Cancer Immunol Immunother, 55 (2006) 900-9.
8. A. Jalili, M. Makowski, T. Switaj, D. Nowis, GM. Wilczynski, E.Wilczek, M. Chorazy-Massalska, A. Radzikowska, W. Maslinski, L. Bialy, J. Sienko, A. Sieron, M. Adamek, G. Basak, P. Mroz, IW. Krasnodebski, M. Jakobisiak, J. Golab, Effective photoimmunotherapy of murine colon carcinoma induced by the combination of photodynamic therapy and dendritic cells, Clin Cancer Res. 10 (2004) 4498-508.
9. H.Saji, W. Song, K. Furumoto, H. Kato, EG. Engleman, Systemic antitumor effect of intratumoral injection of dendritic cells in combination with local photodynamic therapy, Clin Cancer Res. 12 (2006) 2568-74.
10. E-S. Abdel-Hady, P. Martin-Hirsch, M. Duggan-Keen, PL. Stern, JV. Moore, G. Corbitt, HC. Kitchener, IN. Hampson, Immunological and Viral Factors Associated with the Response of Vulval Intraepithelial Neoplasia to Photodynamic Therapy, Cancer Research 61 (2001) 92-196.
11. A. Høgset, L. Prasmickaite, P.K. Selbo, M. Hellum, B.Ø. Engsæter, A. Bonsted, K. Berg, Photochemical internalization in drug and gene delivery, Adv. Drug Del. Rev. 56 (2004) 95-115.
12. A. Dietze, Q. Peng, PK. Selbo, O. Kaalhus, C. Müller, S. Bown, K. Berg, Enhanced photodynamic destruction of a transplantable fibrosarcoma using photochemical internalisation of gelonin, Br. J. Cancer, (2005) 1-6.
13. K. Berg, J. Moan, Lysosomes at photochemical targets. Int. J. Cancer 59, (1994) 814-822.
14. K. Berg, K. Sandvig, J. Moan, Transfer of Molecules into the Cytosol of cells, Patent 1996, PCT/NO95/00149.
15. L. Pasmickaite, A. Høgset, K. Berg, Methods for photochemical transfection: light-induced, site-directed gene delivery, in: J.R. Morgan (Ed.), Meth. Mol. Med., Gene Therapy protocols, vol. 689, Humana Press, Totowa, 2001, 123-135
16. Internal report
17. L.M. Mir, O. Tounekti, S. Orlowski, Bleomycin: revival of an old drug, Gen.Pharmacol. 27 (1996) 745-748.
18. G. Pron, N, Mahrour, S.Orlowski, O. Tounekti, B. Belehradek, J. Belehradek Jr., L.M. Mir, Internalisation of the bleomycin molecules responsible for bleomycin toxicity: a receptor-mediated endocytosis mechanism, Biochem. Pharmacol. 57 (1998) 45-56.

19. K. Berg, A. Dietze, O. Kaalhus, A. Høgset, Site Specific Drug Delivery by Photochemical Internalization Enhances the antitumor effect of bleomycin, Clin. Cancer Res. 11 (2005) 8476-8485.
20. S. Rodriguez-Cuevas, S. Barroso-Bravo, J. Almanza-Estrada, L. Cristobal-Martinez, E. Gonzalez-Rodriges, Electrochemotherapy in primary and metastatic skon tumors: phase II trial using intralesional bleomycin, Arch Med Res., 32 (2001) 273-76.
21. R. Heller, M.J. Jaroszeski, D.S. Reintgen, C.A. Puleo, R.C. DeConti, R.A. Gilbert, L. F Glass, Treatment of cutaneous and subcutaneous tumors with electrochemotherapy using intralesional bleomycin, Cancer 83 (1998) 148-57.
22. D.C. Bloom, P.M. Goldfarb, The role of intratumor therapy with electroporation and bleomycin in the management of advanced squamos cell carcinoma of the head and neck, Eur. J. Surg. Oncl., 31 (2005)1029-1035.
23. G. Sersa, The state-of-the-art of electrochemotherapy before the ESOPE study; advantages and clincal uses, EJC Supplements 4 (2006) 52-59.
24. B. Poddevin, S. Orlowski, J. Belehradek Jr, L.M. Mir, Very high cytotoxicity of bleomycin introduced into the cytocol of cells in culture, Biochem. Pharmacol. 142 Suppl. (1991) 67-75.
25. J. Hay, S Shahzeidi, G. Laurent, Mechanisims of bleomycin-induced lung damage, Arch Toxicol 1991;65:81-94.
26. R. Simon, B. Freidlin, L. Rubinstein, S.G. Arbuck, J. Collins, M.C. Christian, Accelerated titration designs for phase I clinical trials in oncology. J. Natl. Cancer Inst. 89 (1997).
27. JS. Friedberg, R. Mick, J. Stevenson, J. Metz, T. Zhu, J. Buyske, DH. Sterman, HI. Pass, E. Glatstein, SM. Hahn, A phase I study of Foscan-mediated photodynamic therapy and surgergy in patients with mesothelioma, Ann Thorac. Surg 75 (2003) 925-9.

APPENDICES

A Patient information with consent form

B Study flow-chart

C World Medical Association Declaration of Helsinki

D Eastern Cooperative Oncology Group (ECOG) Scale.

E Reponse Evaluation Criteria In Solid Tumors (RECIST)

F Common Terminology Criteria for Adverse Events v 4.0 (CTCAE)

G Fitzpatrick Skin Classification

H Photographs and ultrasound

APPENDIX A PATIENT INFORMATION WITH CONSENT FORM

The Participant Information Sheet and Consent Form complying with ICH E6 / national legislation will be provided for approval by Health Authorities and Ethics Committees/Institutional Review Boards in the UK.

APPENDIX B STUDY FLOW-CHART

All patients will be admitted to hospital from day 0 until day 7. ***Time window: +/- 1 day** ****Time window: +/- 1 week**

Visit number	**Pre-study**	**Base-line**	**1**	**2**	**3**	**4**	**5**	**6**	**7***	**8***	**9***	**10***	**11***	**12***	**13***	**14***	**15***	**16***	**17***	**18****	**19***
TIME SCHEDULE	-14 days [a]	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 9	Day 10	Day 11	Day 12	Day 14	Day 15	Day 21	Day 22	Day 28	Day 29	3 mth	3 mth +1 day
Pat. info and consent	x																				
Inclusion/exclusion	x																				
Medical history & demography	x																				
Pregnancy test	x[c]																				
Enrollment		x																			
Concom. medication /Premedication	x	x[d]				x								x				x		x	
Amphinex adm.		x[e]																			
Bleomycin adm.						x															
Illumination						x															
Vital signs	x	x				x								x				x		x	
Performance status	x	x																x		x	
Adverse events		x				x			x					x				x		x	
Blood safety sample	x[b]	x[b]				x[b]								x[b]				x[b]		x[b]	
Blood, urine test PK		x[l]		x		x			x					x				x		x	
Lesion measurement/ ultrasound		x																x[k]		x[k]	
Photography lesion		x							x					x				x		x	
Pain assessment						x[f]	x[f]														
<u>First</u> patient in each escalated dose group:																					
Fluorescence		x[g]	x	x	x	x		x	x	x		x		x		x[j]		x		x	
Skin Photosen. test		x[g]	x		x			x		x		x		x		x[i]		x[i]		x[i]	
Skin Photosen. Score[h]		x	x	x	x	x		x	x	x	x	x	X	x	x	x[i]	x[i]	x[i]	x[i]	x[i]	x[i]
<u>Subsequent</u> patients in each escalated dose group:																					
Fluorescence		x[g]	x	x	x	x		x	x	x[j]		x[j]		x		x[j]		x		x	
Skin Photosen. Test		x[g]	x		x			x		x[m]		x[m]		X		x[n]		x[n]		x[n]	
Skin Photosen. Score[h]		x	x	x	x	x		x	x	x[m]	x[m]	x[m]	x[m]	x	x	x[n]	x[n]	x[n]	x[n]	x[n]	x[n]

[a] To be performed within 2 weeks of Amphinex administration.
[b] Blood: Haematology and Serum Chemistry
[c] Urine: Pregnancy test for women of child bearing potential
[d] Premedication with steroids and antihistamines (H_1 + H_2 inhibitors) prior to Amphinex administration
[e] Minimum 3 patients in each dose level. See section 3.9 for details of dose escalation.
[f] Pain assessment will be done immediately after illumination and 24 hours after illumination
[g] Test done before Amphinex administration
[h] Skin photosensitivity score done 1 and 24 hours after test when test is performed, including photography to document the reaction
[i] Skin photosensitivity test required if skin reaction is seen on day 14
[j] Fluorescence measurements only done if skin sensitivity test is done at those days
[k] Skin measurements according to RECIST
[l] PK samples before and 30 minutes after and 4 hours after Amphinex administration
[m] Skin photosensitivity test required if skin reaction is seen in the patient on day 6, or at day 9 or later in a previous patient of the same dose group
[n] Skin photosensitivity test required if skin reaction is seen in the patient on day 14, or at day 21 or later in a previous patient

APPENDIX C DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
59th WMA General Assembly, Seoul, October 2008

Can be found at http://www.wma.net/e/policy/pdf/17c.pdf

APPENDIX D EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) SCALE

ECOG Performance Status[a]

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

[a] Oken et al. 1982.

APPENDIX E RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST)

Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Therasse et al. New guidelines to evaluate the response to treatment in solid tumors. J. Natl. Cancer Inst 2000; 92, 205-16). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Efficacy Measures:

Target lesions are all measurable. Target lesions should be selected based upon size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A tumor responder is defined as any patient exhibiting a best study response of PR or CR.

Complete response (CR):	Disappearance of all target lesions.
Partial response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Confirmed at 4 weeks.
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD.
Progressive disease (PD):	At least a 20% increase in the sum of LD of target lesions taking as references the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.

The classification of a response as CR according to RECIST will be made during the statistical analysis process, where the outcome of a second assessment at least 4 weeks after the first will be taken into account.

APPENDIX F COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V 4.0

Common Terminology criteria for adverse events v 4.0 (CTCAE) can be found at
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf

APPENDIX G FITZPATRICK SKIN CLASSIFICATION

Fitzpatrick skin classification

Human skin types / phototypes and their reactivity to sunlight

Skin phototype history	Unexposed skin colour	MED range mJ/cm2	Sensitivity to UVR	Sunburn and tanning
I	White	15-30	Very sensitive	Always burns easily, never tans
II	White	25-40	Very sensitive	Always burns easily, tans minimally
III	White	30-50	Sensitive	Burns minimally,tans uniformly (light brown)
IV	Light brown	40-60	Moderately sensitive	Burns minimally, always tans well (moderate brown)
V	Brown	60-90	Minimally	Rarely burns (dark brown)
VI	Dark brown or black	90-150	Insensitive or least sensitive	Never burns deeply (black)

APPENDIX H

PHOTOGRAPHS

Photographs will be taken of the target lesion areas included in the study at baseline before treatment and at the follow-up visit at day 14, 28 and at 3 months. These photographs should be of high quality and result in paper copies. Next to the lesion a ruler with a millimetre scale will be attached to the skin. This ruler will also present the identification of the subject, i.e. subject number, date and field number. PCI Biotech AS will supply these adhesive rulers.

The photographic procedure will be as follows:
Baseline: Take an overview picture of the area to be treated. Take close-up photos of each field, including the ruler available as an adhesive tape (identifying patient number and date of visit). The photos taken should ensure that the investigator will be able to locate the lesions at the response assessment visit. A transparent grid might be included in some photos to guide the positioning of the grid at the response assessment visit.
Study Visit 8, 11 and 12 (Day 14, 28 and 3 month): Use the previous photos treated area, to aid in making identical photos with regards to light and distance. Repeat the procedure as described above for baseline photos. As soon as the prints are developed and returned, put them (with patient identification) in plastic folders.

ULTRASOUND

Target lesions will be measured using ultrasound unless the investigator feels that ultrasound would not provide significant additional information, due to the size, location, or nature of the lesion. In such cases the lesion will be measured by surface measurement. Target lesions should be selected based upon size (lesions with the longest diameter) and their suitability for accurate repetitive measurements. Ultrasound measurements should be documented by a print-out of the measurement.

A tumor responder is defined as any patient exhibiting a best study response of PR or CR.

Complete response (CR):	Disappearance of all target lesions.
Partial response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions taking as reference the baseline sum LD. Confirmed at 4 weeks.
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