Clinical Study Protocol

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A Phase I, Open Label, Multicenter Study to Assess the Safety, Tolerability and Pharmacology of AZD2281 in Combination with Liposomal Doxorubicin (Caelyx®) in Patients with Advanced Solid Tumors

Sponsor:

[redacted]

Date

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
01	[redacted]		

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change
01	[redacted]		
02	[redacted]		

ASTRAZENECA PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

In the case of an emergency you may contact the Study Delivery Team Leader. If the Study Delivery Team Leader is not available, contact the Study Delivery Team Physician at the AstraZeneca site shown below. In case of a medical emergency you may use the contact details in Section 9.

Role in the study	Name	Address and Telephone number
Study Delivery Team	[redacted]	[redacted]

For further clarifications regarding:

- Procedures in case of medical emergency see Section 9.2
- Procedures in case of overdose see Section 9.3
- Procedures in case of pregnancy see Section 9.4

PROTOCOL SYNOPSIS

A Phase I, Open Label, Multicenter Study to Assess the Safety, Tolerability and Pharmacology of AZD2281 in Combination with Liposomal Doxorubicin (Caelyx®) in Patients with Advanced Solid Tumors

International Coordinating Investigator and Principal Investigator Switzerland

[redacted]

Study centre(s), type and number of subjects planned

The study will be an open label, multicenter, dose finding study. Depending on the tolerated dose up to 7 dose levels will be explored in this study, approximately 33 patients (21-54 depending on number of cohorts) may be enrolled into this study. Three patients will be initially dosed in each cohort.

Study period		Phase of development
Estimated date of first subject enrolled	[redacted]	Phase I
Estimated date of last subject completed	[redacted]	

Objectives

The primary objective of this study is

1. To determine the recommended dose (RD) of twice daily oral doses of AZD2281 either as intermittent therapy for 7 days out of a 28-day schedule or given continuously, administered in combination with liposomal doxorubicin to patients with advanced solid tumors.

The secondary objectives are

1. To investigate the pharmacokinetic (PK) interaction of AZD2281 with liposomal doxorubicin. The exposure to AZD2281 when given alone or in combination with liposomal doxorubicin will be compared by assessment of appropriate derived PK parameters at cycle 1.

2. To investigate the pharmacokinetic (PK) of AZD2281: in the dose finding part the PK will be characterized by a limited sampling PK profile while, in the expansion part at the recommended dose (RD), a full PK profile will be performed. (Figure 1)

3. Two different schedules of administration of AZD2281 will be tested.
   Schedule 1: AZD2281 bid for 7 days (day 1-7) out of a 28-day schedule. (For PK evaluation AZD2281 will be given on day 2-8 at cycle 1 only.)
   Schedule 2: AZD2281 bid continuously for a 28-day schedule.

The exploratory objective is

1. To investigate the effects of the combination on DNA repair mechanisms by the determination, in isolated peripheral blood mononuclear cells (PBMCs), of histone H2AX phosphorylation, a marker of DNA damage and induction of DNA repair.

Study design

This will be a Phase I, open label, multicenter, dose finding study to evaluate the safety, tolerability and pharmacokinetic of twice daily oral dosing with AZD2281 (given for 7 days or continuously) when administered in combination with liposomal doxorubicin (Caelyx, 40 mg/m^2) given every 28 days to patients with advanced solid tumors. A design of concerted escalation of dose and dosing duration will be applied according to which the shorter schedule (7 day-dosing) is tested first; if proven tolerable, the tolerability of the same dose given for 4 weeks is assessed while the tolerability of a higher dose given for 7 days is assessed concomitantly (Figure 2). According to this design, the 1-week schedule, potentially more toxic but also more easily monitored, is driving the dose schedule. This design could increase the accrual of patients and could shorten the duration of the study, while preserving patient safety (Sessa et al 2007) (Figure 2)

Potentially up to 7 dose levels of AZD2281 will be explored in this study. In a pilot phase, 50mg twice daily for 1 week will be given, if MTD has not been reached, the main trial will be performed with 100 mg, 200 mg and 400 mg (twice daily for 1 week or continuous dosing) in order to confirm the dose levels that can be tolerated with liposomal doxorubicin. Patients

with confirmed eligibility will be initially enrolled into cohort 1. At the end of the first cycle of the patients of each cohort, a safety review of the data will be performed.

Pilot Dose level (AZD2281 50 mg twice daily plus 40mg/m^2 Caelyx)

Three patients will be initially treated at AZD2281 doses of 50 mg bid:

One dose of 50 mg AZD2281 on day 1 followed by 50 mg twice daily on day 2-8 plus Caelyx 40 mg/m2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

- If no DLT within the first cycle, proceed to dose level of Cohort 1
- If 1 DLT within the first cycle, expand by 3 patients, if no further DLT, proceed to dose level of Cohort 1
- If ≥2 DLT within the first cycle in 6 patients, dose is considered not tolerable.

Cohort 1

One dose of 100 mg AZD2281 on day 1 followed by 100 mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 2

Continuous dosing of 100 mg AZD2281 twice daily plus Caelyx 40 mg/m^2 on day 1 of a 28-day cycle

Cohort 3

One dose of 200 mg AZD2281 on day 1 followed by 200 mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 4

Continuous dosing of 200 mg AZD2281 twice daily plus Caelyx 40 mg/m^2 on day 1 of a 28-day cycle

Cohort 5

One dose of 400 mg AZD2281 on day 1 followed by 400mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 6

Continuous dosing of 400 mg AZD2281 twice daily plus Caelyx 40 mg/m^2 on day 1 of a 28-day cycle

3 patients will be dosed in each cohort initially:

- If no DLT within the first cycle, proceed to next dose level
- If 1 DLT within the first cycle, expand by 3 patients, if no further DLT, proceed to next dose level
- If ≥2 DLT within the first cycle in 6 patients, dose is considered not tolerable.

Recommended dose: MTD will be considered to have been exceeded if ≥2 DLT within the first cycle of treatment in 6 patients occurred, and the 2 lower cohorts will then be expanded up to a maximum of 12 patients to confirm the recommended dose (RD). By choosing the 2 lower cohorts, they can then be compared in terms of toxicity and biological effects (pharmacodynamic marker). It could be that the higher dose for a shorter period is as effective as the lower dose given continuously and is better tolerated or vice versa. If MTD occurs at cohort 1, study is being closed, if MTD occurs at cohort 2, only cohort 1 will get expanded.

Pharmacokinetic: Pharmacokinetic sampling will be performed to collect single dose data of AZD2281 alone and of both drugs when given in combination. A further one or two (intermittent and continuous therapy respectively) plasma samples will be collected to provide a measure of multiple dose exposure to AZD2281 in combination with liposomal doxorubicin. Dosing with liposomal doxorubicin will commence on day 1 (cohorts 2, 4, 6) or on day 2 (cohorts pilot, 1, 3, 5). Patients are required to complete at least 1 cycle of liposomal doxorubicin treatment (28 days). A full PK profile for AZD2281 and doxorubicin will be taken for patients entering the expansion phase of the trial on the day of first administration of liposomal doxorubicin.

Investigational product, dosage and mode of administration

The doses of AZD2281 will be made up from 50 mg capsules to be taken orally twice daily. Patients should swallow the medication whole with a glass of water in the morning and in the evening at the same time each day. This is to ensure approximately a 12-hour interval between doses. Due to the potential impact of food on absorption of AZD2281, patients should not eat for at least one hour before taking the dose and they should then refrain from eating for at least 2 hours after each dose. Liposomal doxorubicin (Caelyx®) will be administered by intravenous infusion at a dose of 40 mg/m^2 given every 28 days. The initial doxorubicin dose should be administered at a rate no greater than 1mg/minute. If no infusion reaction is observed, subsequent Caelyx infusions may be administered over a 60-minute period.

Duration of treatment

The duration of AZD2281 and liposomal doxorubicin combination treatment will be 56 days (until the end of the second cycle), assuming patients do not meet a withdrawal criterion before that time. However, patients who show an objective response (RECIST criteria) may continue combinational study treatment in the originally assigned cohort until they meet a

withdrawal criterion or until a maximum duration of total 6 cycles have been reached. Patients with stable disease who, in the investigator's opinion, receive some benefit from the therapy and do not meet a withdrawal criterion may, at their own wish, continue with AZD2281 as monotherapy in the originally assigned cohort. Patients with progressive disease or intolerable toxicity will get further treatment at the discretion of the investigator.

Safety data will be assessed for all patients during AZD2281 therapy.

Variables

- Safety
  - Adverse events
  - Vital signs including blood pressure (BP) and pulse rate (PR)
  - ECG and LVEF (by echocardiography or MUGA)
  - Haematology
  - Clinical chemistry
  - Urinalysis
  - Physical examination
- Pharmacokinetic
  - C_{max}, t_{max}, AUC_{0-10h}, C_{min}
- Pharmacodynamic
  - Histone H2AX phosphorylation level in PBMCs.

Statistical methods

The primary objective of this study is to assess the recommended dose of AZD2281 when given in combination with liposomal doxorubicin. There will be no formal statistical analysis of safety and tolerability data. Data will be listed and summarised.

PK data will be analysed by non-compartmental methods and for AZD2281 the parameters C_{max}, t_{max}, AUC_{0-10h} and C_{min} will be calculated. There will be no formal statistical analysis of the PK variables. All pharmacokinetic variables will be summarised and listed.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
ADP	Adenosine diphosphate
AE	Adverse event (see definition in Section 5.7)
ALP	Alkaline Phosphatase
ANC	Absolute neutrophil count
APTT	Activated Partial Thromboplastin time
AST	Aspartate Transaminase (SGOT)
AUC_{0-10}	Area under the plasma concentration-time curve to 10 hours after dosing
bid	Twice daily
BER	Base excision repair
BP	Blood pressure
BRCA	Breast cancer gene (type)
C_{max}	Maximum plasma (peak) concentration in plasma
C_{min}	Minimum plasma (trough) concentration in plasma
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CT	Computerised tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DSB	Double Strand Break
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte/macrophage colony-stimulating factor
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio

Abbreviation or special term	Explanation
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IEC	Independent Ethics Committee
IRB	Independent Review Board
LVEF	Left ventricular ejection fraction
MRI	Magnetic Resonance Imaging
MUGA scan	Multi-gated acquisition scan
NAD	Nicotine adenine dinucleotide
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment)
ORR	Objective Response Rate
PAR	Poly-(ADP-ribose)
PARP	Poly (ADP-ribose) polymerase
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
PPE	Palmar-plantar erythrodysesthesia
PR	Partial response
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event (see definition in Section 5.7).
SAP	Statistical Analysis Plan
SD	Stable disease
SSAR	Suspected Serious Adverse Reaction
SSB	Single Strand Break
SUSAR	Suspected Unexpected Serious Adverse Reaction
Study medication	Refers to both drug(s) under investigation administered as part of the schedule
TBD	To be decided
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
TTP	Time To Progression
UPN	Unique Patient Number
WBC	White Blood Cells

1. INTRODUCTION

1.1 Background

1.1.1 PARP and PARP-1 inhibition

Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] or PAR polymerisation is a unique post-translational modification of histones and other nuclear proteins that contributes to the survival of proliferating and non proliferating cells following deoxyribonucleic acid (DNA) damage. This event represents an immediate cellular response to DNA damage and involves the modification of glutamate, aspartate and lysine residues with the addition of long chains of Adenosine diphosphate (ADP)- ribose units, derived from Nicotine adenine dinucleotide (NAD)+, onto the DNA binding proteins. The enzymes that catalyse this process, poly (ADP-ribose) polymerases (PARPs), are critical regulatory components in DNA damage repair and other cellular processes. They now comprise a large and expanding family of 18 proteins, encoded by different genes and displaying a conserved catalytic domain in which PARP-1 (113 kDa), the initial member, and PARP-2 (62 kDa) are so far the sole enzymes whose catalytic activity has been shown to be immediately stimulated by DNA strand breaks. Moreover, many of the identified family members interact with each other, share common partners and common sub-cellular localizations suggesting functional redundancy and possibly fine-tuning in the regulation of post translational modification of proteins.

The range of biological roles involving PARP proteins is wide. This includes DNA repair and maintenance of genomic integrity, regulation of protein expression at the transcriptional level, regulation of cellular replication and differentiation, regulation of telomerase activity, involvement in cell elimination pathway by necrosis and serving as a signal for protein degradation in oxidatively injured cells (Virag and Szabo 2002).

Of the various members of the PARP enzyme family, only PARP-1 and PARP-2 work as DNA damage sensor and signaling molecules. PARP-1 is a nuclear enzyme consisting of 3 domains, the N-terminal DNA-binding domain containing 2 zinc fingers, the auto-modification domain and the C-terminal catalytic domain. It binds to both single and double-stranded DNA breaks through the zinc-finger domain. PARP-1 catalyses the cleavage of NAD+ into nicotinamide and ADP-ribose, the latter is then synthesised to form branched nucleic acid-like polymers covalently attached to nuclear acceptor proteins. This branched ADP-ribose polymer is highly negatively charged, thereby affecting the function of the target proteins. Histones have been found to be acceptors of poly ADP-ribose, the negative charge leads to electrostatic repulsion between DNA and histones. This has been implicated in chromatin remodelling, DNA repair and transcriptional regulation. Other transcriptional factors and signalling molecules shown to be poly-ADP-ribosylated by PARP-1 are nuclear factor-κB, DNA-dependent protein kinase, p53, topoisomerase-I, lamin B and PARP-1 protein itself (Virag and Szabo 2002).

PARP-1 activation leads to DNA repair through the base excision repair (BER) pathway, and cells deficient in PARP-1 have been shown to have delayed DNA repair function. Like

PARP-1, PARP-2 also responds to DNA damage and will similarly lead to single strand DNA repair. For both proteins inactivation and cleavage promotes apoptosis and is part of the apoptotic cascade. Loss of PARP-1 activity in cells or in knockout mice leads to both radio- and chemo-sensitisation. Moreover, increased PARP-1 activity has been found in many tumor types. The use of PARP inhibitors, like the knockout studies, has confirmed that in combination an enhancement of the antitumor activity of radiation and DNA damaging cytotoxics occurs (Virag and Szabo 2002) and (Nguewa et al 2005).

1.1.2 Homologous recombination deficiency and PARP

AZD2281 (previously referred to as KU 0059436 in earlier studies) is an inhibitor of PARP-1 and shows monotherapy activity in tumor cells with defective components of homologous recombination, which includes cells with the BRCA1-/- and BRCA2-/- genotype. Due to the molecular targeting of AZD2281 to specific subsets of tumors, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP-1 inhibitor compared with conventional treatments such as chemotherapy. AZD2281 displays anti tumor activity to a variety of tumor cell lines and this sensitivity of the cells is known, in some instances and believed in others, to depend upon components of a defective homologous recombination capability. As a major example of this selective activity, the breast cancer (BRCA)-/- gene tumors (both BRCA1 and BRCA2) are seen to be highly sensitive to PARP inhibition. Recent studies indicate that PARP inhibition in BRCA1 and BRCA2 homozygous null cells, but not the isogenic BRCA heterozygous cells, leads to selective cell death. The BRCA1 and 2 genes encode proteins that are implicated in homologous DNA strand break repair, known as homologous recombination. BRCA1 or BRCA2 dysfunction profoundly sensitises cells to PARP inhibition leading to chromosomal instability, cell cycle arrest and apoptosis (Farmer et al 2005). This sensitivity compared to unaffected heterozygous tissue provides a large therapeutic window for PARP inhibition.

1.1.3 Epigenetic suppression of the breast cancer (BRCA) gene

“BRCAness” is the term given to the phenotype that some sporadic tumors share with familial-BRCA cancers. Epigenetic mechanisms of gene inactivation are well recognised to result in silencing of tumor-suppressor genes. Aberrant methylation of the BRCA1 promoter is found in 11-14% of sporadic breast cancers, primarily in the basaloid “triple negative” (ER , PR , HER2) breast cancers, and in 5-31% of ovarian cancers. This phenotype may also be present in cervical, head and neck and prostate cancers. Identification of the BRCAness phenotype has been reported to portend clinical benefit from drug therapy inducing DNA-damage (Turner et al 2004). Recently, deficiencies in a number of additional components of the homologous recombination repair pathway have also been demonstrated to confer sensitivity to PARP inhibition (McCabe et al 2006). Moreover, inactivation of a number of these components has been reported in a range of solid tumors. For example, the Fanconi anaemia proteins that are also involved in DNA repair processes, have been shown to be inactivated in lung, oral cancer and cervical cancer cell lines by promoter hypermethylation, rendering these cells highly sensitive to DNA cross-linking agents including platinum-based therapies (Marsit et al 2004; Narayan et al 2004). Recent evidence indicating sensitivity of BRCA1 and BRCA2 deficient cells to PARP inhibition suggests that epigenetic modification

of the Fanconi anaemia/BRCA pathway may also lead to activity of PARP inhibitors in these tumor types.

1.2 Relevant preclinical results

The pre-clinical experience is fully described in the Investigator's Brochure. Key findings are summarised below.

The AZD2281 molecule shows cellular activity in the low nM range with a cellular dose for 50% inhibition (IC50) of ~2nM in HeLa cells.

Pharmacokinetic data for the rat showed sex differences in absorption parameters for individual studies. However, these observations were variable and, as no gender difference in PK parameters was seen in the dog, it seems unlikely that these are of relevance to the proposed clinical study. Higher systemic exposure in female rats compared with males at the same dose level accounts for their apparently greater sensitivity to the drug, as seen by haematological and histological changes in the toxicology studies. In the dog, toxicokinetics were similar for males and females.

Distribution of AZD2281 is typical for an orally administered foreign compound, in the gastro intestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Metabolism data to date is limited and further investigations are ongoing. To date, several metabolites have been observed in pre clinical studies, although their identification and activity have yet to be confirmed. Similar metabolite profiles were observed in the urine and faeces of male and female rats. Excretion is primarily via the faeces and, to a lesser extent, the urine. In a study of [^{14}C] AZD2281 in the rat, excretion was 76±13% in faeces and 20±11% in urine.

1.2.1 Summary of toxicological data

AZD2281 has been tested in a standard range of safety pharmacology studies ie, dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetized dog or any behavioural, autonomic or motor effects in the rat at the doses studied.

The toxicology studies indicate that the target organ of toxicity is the bone marrow. Specific ex vivo work has been conducted exposing human bone marrow cells to AZD2281, which has confirmed that AZD2281 is also active against human marrow. However, the cytotoxic effect becomes evident at a higher concentration than that which fully ablates PARP activity (mean IC50 of 2.7 μM for myelosuppression in n=4 human donors compared with 0.1 μM for total PARP-1 activity inhibition). These data along with the 28 day dog and rat studies, show a myelotoxic effect that is mild to moderate and is reversible. Platelets appear first affected, followed by white blood cells. Twenty six week repeat oral dose studies of AZD2281 in rat and dog have given similar results, with the drug being well tolerated and no drug related mortality. Importantly, oncology clinics are well used to monitoring for the onset of such effects and are expert in their management.

AZD2281 showed no mutagenic potential in the Ames test, was clastogenic in the Chinese Hamster Ovary chromosome aberration test, and was genotoxic in the rat micronucleus test. These findings are not uncommon for many therapeutic agents used in oncology and so do not present an unacceptable risk when appropriately clinically managed.

In the male fertility study in the rat, administration of AZD2281 to male rats at doses of 5, 15 or 40 mg/kg/day prior to puberty and throughout spermatogenesis had no adverse effect on mating performance, fertility, embryonic survival, sperm parameters, male reproductive tract organ weights or histological appearance of testes or epididymides. Dosing males with 15 or 40 mg/kg/day resulted in dosage-related slight toxicity. Dosing with males 5 mg/kg/day caused no significant effects.

In the embryofoetal development study in the rat, administration of AZD2281 to female rats during the period of major embryonic organogenesis at a dose of 0.5 mg/kg resulted in slight maternal toxicity. There was no effect on pregnant animals after dosing with 0.05 mg/kg/day. After dosing with 0.5 mg/kg/day, early embryofoetal survival and foetal weights were reduced with the occurrence of major eye and vertebral/rib malformations and increased incidences of several visceral and skeletal minor abnormalities and variants. After dosing with 0.05 mg/kg/day, there was an associated increased incidence in a minor visceral abnormality and skeletal variant. There was also one foetus with a major eye malformation. A "no observed adverse effect" dose level for foetal abnormalities was not established.

1.3 Summary of clinical experience

The clinical experience with AZD2281 is fully described in the Investigator's Brochure. As of 21 November 2007, an estimated 205 patients have been recruited into 4 ongoing monotherapy studies and 4 studies in combination with one of the following chemotherapy agents; dacarbazine, gemcitabine, carboplatin or topotecan. The first clinical study in man (KU36-92) is a dose-escalation study in patients with advanced solid tumors. To date, in this ongoing study, 86 patients have been exposed to AZD2281 and have received doses from 10 mg od up to 600 mg bid, the dose at which dose-limiting toxicity (DLT) was observed. Of these 86 patients, 8 have received AZD2281 for 6-12 months and one patient has been on treatment for >12 months. The other studies have only begun to recruit patients recently and safety data from the clinical database is not yet available.

Preliminary efficacy data are available from 21 patients with hereditary BRCA-associated ovarian cancer from study KU36-92. A significant clinical response has been observed in 9 (43%) of these 21 patients, based on assessment of Response Evaluation Criteria in Solid Tumors (RECIST) for 7 patients and by cancer antigen (CA-125) levels for 2 patients. Several patients have shown a confirmed response in excess of 30 weeks and in many of the patients the response is ongoing.

In addition to the responses in patients with ovarian cancer, 3 non-BRCA patients (pleural sarcoma, renal carcinoma and NSCLC), dosed at 10 mg/day, 40 mg/day and 200 mg/day, respectively, achieved stable disease for >4 months.

Preliminary unvalidated safety data from 61 patients is available from study KU36-92. Key Safety findings from these data indicate that AZD2281 monotherapy is generally well tolerated at doses up to an including the maximum tolerated dose of 400 mg bid in patients with various solid tumors. Dose limiting toxicity was observed at 600 mg bid.

As expected in patients with advanced cancer, 98% of the patients experienced at least one adverse event. In total, 77% experienced at least one adverse event that the investigator attributed to study medication. The number of patients reported to have drug related AE by the investigator increased with increasing dose from approximately two-thirds of patients at doses ≤100 mg bid to all 4 patients in the 600 mg bid. dose group. Most of the AEs were mild to moderate in intensity. The number of patients with CTC grade 3 or 4 events attributed to trial medication by the investigator was low (14.8% overall) and increased with increasing dose. The number of patients with AEs leading to discontinuation of treatment was generally low (27.8%), with only one patient in each of the 200 mg, 400 mg groups and 2 patients at the 600 mg dose discontinuing treatment due to events considered by the investigator to be attributed to study drug (6.6%). Five patients died as a result of an AE, from the following AZD2281 dose groups; 2 at ≤100 mg, 2 at 200 mg and 1 at 400 mg bid. In none of these patients was the fatal event considered by the investigator be related to AZD2281. Two patients died due to general physical deterioration in their condition, one due to pulmonary embolism, and 2 patients died due to infection (non-neutropenic sepsis and a chest infection).

Many of the AEs reported, such as anorexia, weight decreased, cough, dyspnoea, nasopharyngitis (common cold), peripheral oedema and arthralgia are frequently seen in patients with advanced tumors due to their underlying disease, co-morbidity and concomitant medications. Furthermore, urinary tract infection, abdominal pain, back pain, diarrhoea and constipation commonly occur in patients with widespread intra-abdominal tumor involvement such as in sigmoid/colon and ovarian cancers. The most common AEs reported (in 15 patients, ~25% of patients) were nausea (49%), vomiting (39%), fatigue (44%), anorexia (26%), and tachycardia (36%).

Following ongoing safety surveillance processes internal to AstraZeneca, AZD2281 is considered associated with the following events (see ‘Emerging Safety Profile’ Section 5.4 of the Investigator’s Brochure):

- Laboratory findings and/or clinical diagnosis of:
  - Anaemia, generally mild to moderate (CTC grade 1 or 2)
  - Neutropenia, predominantly mild to moderate (CTC grade 1 or 2)
  - Thrombocytopenia, generally mild to moderate (CTC grade 1 or 2), sometimes severe (CTC grade 3 or 4)
- Nausea and vomiting, generally mild to moderate (CTC grade 1 or 2), intermittent and manageable on continued treatment

- Fatigue, generally intermittent of mild to moderate intensity (CTC grade 1 or 2).

These events will continue to be monitored to assess frequency and severity as patient exposure increases.

Overall, ~36% of patients reported mild (CTC grade 1), asymptomatic tachycardia. All events were considered by the investigator to be unrelated to study drug, and none required treatment. There was no evidence of a dose-related increase in pulse, and review of the cases provided no evidence of drug-induced cardiotoxicity. Relevant medical histories or observations made at physical examination and concomitant medications offered alternative explanations for the observed tachycardia. Based on the available data, the Sponsor considers there is insufficient evidence to suggest a causal association between treatment with AZD2281 and tachycardia.

As part of ongoing pharmacovigilance, a safety review of events considered associated with alterations in cognitive performance (which included reported events of somnolence, dizziness, depression, cognitive disorder, attention/mental impairment and memory impairment) has recently been conducted. Cognitive disorders are among the most frequent psychiatric complications of advanced cancer. Preclinical data with AZD2281 has shown no evidence of a pharmacological or toxicological effect of AZD2281 on cognitive function.

The majority of patients were receiving concomitant medications reported to cause these types of events and some patients had brain metastases and other co-morbidities (eg, hypertension, epilepsy) that may offer an alternative explanation for the events. Based on the limited data available to date, the Sponsor considers there is insufficient evidence to suggest a causal association between alterations in cognitive performance and AZD2281 treatment. However, this safety topic will be kept under close surveillance as part of ongoing pharmacovigilance activities.

Dose-limiting toxicity was observed at the 600 mg bid. dose in this study. Two patients experienced events that were defined as Dose-Limiting Toxicity. The first patient with mesothelioma experienced CTC grade 4 thrombocytopenia, without any evidence of bleeding. The second patient with breast cancer experienced CTC grade 3 somnolence. The maximum tolerated dose was defined in this study as 400 mg bid.

1.4 Pharmacokinetic background

1.4.1 AZD2281

The elimination pathways for AZD2281 in man have not yet been defined. The only available data are from preclinical studies. Preclinical studies in rats and dogs showed AZD2281 is extensively metabolised with faecal excretion being the predominate route of elimination.

In rats there appeared to be a sex difference in the pharmacokinetics and metabolism of AZD2281. In male rats, circulating plasma concentrations of parent compound, and the amount of drug excreted as unchanged AZD2281 in the urine, was lower than in female rats. Correspondingly the proportion of the dose excreted as metabolites into the bile was higher in

male rats than females. Hydroxylation and oxidation reactions were the primary metabolic pathways undertaken by AZD2281 following administration to rats. In both rats and dogs the excretion of [^{14}C]-AZD2281 was essentially complete 24 to 48 hours after dosing.

From in-vitro data, the most important routes of AZD2281 metabolism appear to be mediated by CYP3A4.

Preliminary pharmacokinetic data are available from patients following both single and multiple oral doses to patients. Following administration of a single oral dose of AZD2281 at doses of 10 to 600 mg, absorption of AZD2281 was relatively rapid with maximum plasma concentrations achieved in the majority of cases between 1 and 3 hours after dosing. Following the peak, plasma concentrations declined biphasically with a terminal half-life (based upon sampling to 24 hours after dosing) of between approximately 5 and 7 hours. The exposure achieved (C_{max}, AUC_{0-10}, AUC_{0-24} or AUC), increased with increasing dose at doses up to 100 mg but began to plateau as the dose was increased further. Within each dose group, exposure parameter values typically covered a 2- to 3-fold range. The mean volume of distribution of AZD2281 was 39.9 L and mean plasma clearance was 76 mL/min (in both cases these mean values have been calculated from data obtained at dose levels between 10 and 80 mg).

Following daily administration of 10, 20, 40 or 80 mg AZD2281 to patients for 14 days, absorption was rapid (tmax typically between 1 and 3 hours). The derived terminal half-life (based upon sampling to 48 hours after dosing) was between 7 and 13 hours. Consistent with the terminal half-lives, exposure did not increase markedly (approx 20%) over that achieved following a single dose. Comparison of AUC_{0-24} on day 14 with AUC following the single dose showed, that for the majority of the patients where this comparison was possible (12 out of 14), AUC_{0-24} on day 14 was within approximately 30% of that expected from the single dose data suggesting no marked time dependency in the pharmacokinetics of AZD2281. Following twice daily administration of 60, 100, 200, 400 and 600 mg of AZD2281 to patients for 14 days, C_{max} and AUC_{0-12} increased by an average of 25 and 41%, respectively (ranges 0.65 to 2.1; 0.60 to 2.2, respectively).

1.4.2 Liposomal doxorubicin

The pharmacokinetics of Caelyx was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of Caelyx over the dose range of 10 mg/m^2 to 60 mg/m^2 was best described by a two compartment non-linear model with zero order input and Michaelis-Menten elimination. The mean intrinsic clearance of Caelyx was 0.030 l/h/m^2 (range 0.008 to 0.152 l/h/m^2) and the mean central volume of distribution was 1.93 l/m^2 (range 0.96 – 3.85 l/m^2) approximating the plasma volume. The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours.

1.5 Rationale

Poly (ADP-ribose) polymerise PARP is a nuclear enzyme that signals the presence of DNA damage by catalysing the addition of ADP-ribose units to DNA, histones and various DNA repair enzymes and by facilitating DNA repair. Enhanced PARP-1 expression and activity has been demonstrated in a number of tumor cell lines (Ratnam and Low 2007). AZD2281 is a member of an emerging class of orally administered PARP inhibitors currently in clinical development. PARP is overexpressed in a variety of tumors and is the main enzyme responsible for the Base Excision Repair (BER) mechanism involved in the repair of cisplatin induced DNA damage. In the presence of BRCA1-2 mutations, with defects in recombination repair, the administration of PARP inhibitors could result in Double Strand Breaks (DSB) with cell death. PARP inhibitors can be also effective in case of other homologous recombination defects with DSB.

Agents that inhibit PARP have the potential to improve the therapeutic efficacy of several commonly used chemotherapeutics in oncology. Previous and ongoing studies to date with AZD2281 have demonstrated inhibition of PARP over a range of doses with evidence of clinical efficacy and an acceptable safety and tolerability profile. AZD2281 appears to be generally well tolerated at PARP inhibitory dose levels in non-clinical toxicological testing and in the ongoing Phase I clinical study (KU36-92). Thus it represents a potential means of obtaining therapeutic advantage by directly inhibiting PARP-1 and hence tumor growth, either when used as monotherapy or in combination therapy with other cytotoxic agents. Single agent AZD2281 has already shown antitumor efficacy in patients with ovarian cancer who have failed previous treatment with platinum; the antitumor activity was significant in both groups of platinum sensitive and, even though to a lower extent, platinum resistant patients.

Liposomal doxorubicin (Caelyx®) is standard second / third line treatment in patients failing platinum and taxanes, with a confirmed objective response rate of around 30% in platinum sensitive, and <10% in platinum resistant patients. Liposomal doxorubicin, like other anthracyclines, causes Single Strand Breaks (SSB) and DSB mediated by both DNA topoisomerase II enzyme and by free oxygen radical formation.

Therefore combination with PARP seems to be particularly promising because of the synergistic biological effect against DNA, the lack of potential overlapping toxicities and the clinical application in tumor types with predisposing mutations or in which platinum resistance is a problem of clinical relevance.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is

1. To determine the recommended dose (RD) of continuous twice daily oral doses of AZD2281 when administered in combination with liposomal doxorubicin to patients with advanced solid tumors.

2.2 Secondary objective(s)

The secondary objectives of the study are:

1. To investigate the pharmacokinetic (PK) interaction of AZD2281 with liposomal doxorubicin. The exposure to AZD2281 when given alone or in combination with liposomal doxorubicin will be compared by assessment of appropriate derived PK parameters at cycle 1.

2. To investigate the pharmacokinetic (PK) of AZD2281: in the dose finding part the PK will be characterized by a limited sampling PK profile while, in the expansion part at the recommended dose (RD), a full PK profile will be performed (Figure 1).

3. To test two different schedules of administration of AZD2281.
   Schedule 1: AZD2281 bid for 7 days (day 1-7) out of a 28-day schedule. (For PK evaluation AZD2281will be given on day 2-8 at cycle 1 only).
   Schedule 2: AZD2281 bid continuously for 28 days.

The exploratory objective is:

1. To investigate the effects of the combination on DNA repair mechanisms by the determination, in isolated PBMCs, of histone H2AX phosphorylation, a marker of DNA damage and induction of DNA repair.

3. STUDY PLAN AND PROCEDURES

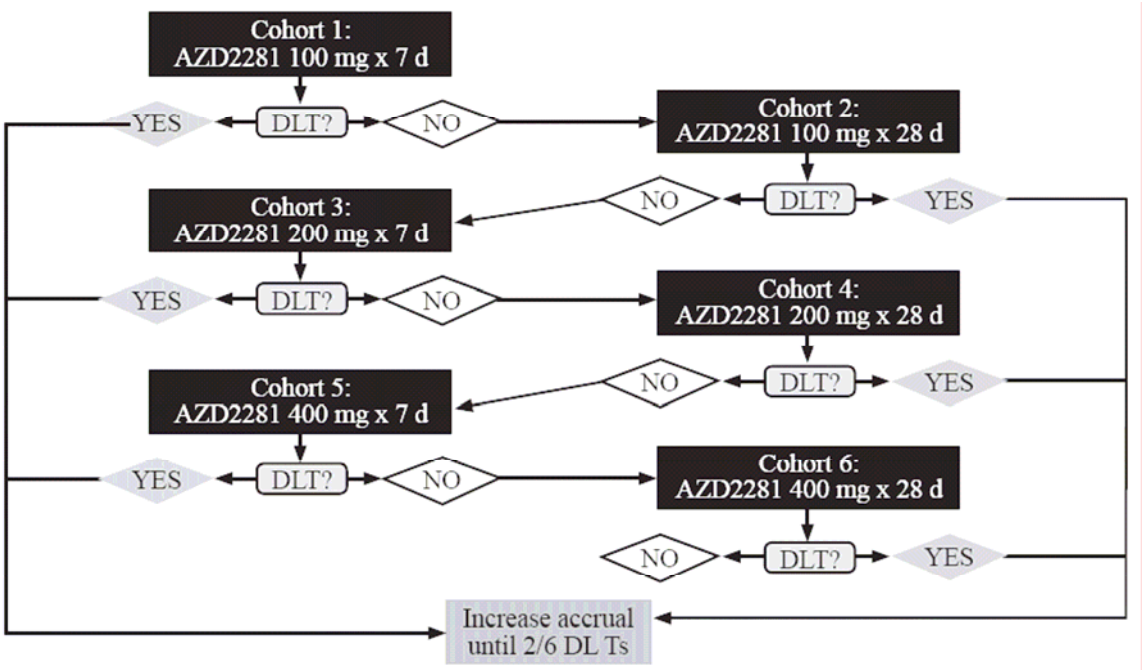
3.1 Overall study design

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This will be a Phase I, open label, multicenter, dose finding study to evaluate the safety, tolerability and pharmacokinetics of twice daily oral dosing with AZD2281 when administered in combination with liposomal doxorubicin (Caelyx, 40 mg/m^2) given every 28 days to patients with advanced solid tumors. Potentially up to 6 dose levels of AZD2281 will be explored in this study: 100 mg, 200 mg and 400 mg (twice daily for 1 week or continuous dosing) in order to confirm the dose levels that can be tolerated when AZD2281 is given with liposomal doxorubicin (Figure 1 and section 4.4.2). A design of concerted escalation of dose and dosing duration will be applied according to which the shorter schedule (7 day-dosing) is being tested first; if proven tolerable, the tolerability of the same dose given for is assessed while the tolerability of a higher dose given for 7 days is assessed concomitantly (Figure 2). According to this design, the 1-week schedule, potentially more toxic but also more easily monitored, is driving the dose schedule. This design could increase the accrual of patients and could shorten the duration of the study, while preserving patient safety (Sessa et al 2007) (Figure 1).

Pharmacokinetic: Pharmacokinetic sampling will be performed to collect single dose data of AZD2281 alone and of both drugs when given in combination. A further one or two (intermittent and continuous therapy respectively) plasma samples will be collected to provide a measure of multiple dose exposure to AZD2281 in combination with liposomal doxorubicin. Dosing with liposomal doxorubicin will commence on day 1 (cohorts 2, 4, 6) or on day 2 (cohorts pilot, 1, 3, 5) at cycle 1. From cycle 2 onwards, liposomal doxorubicin will be given on day 1 in all cohorts. Patients are required to complete at least 1 cycle of liposomal doxorubicin treatment (28 days). A full PK profile for AZD2281 and doxorubicin will be taken for patients entering the expansion phase of the trial. See Table 2 for details of blood collection.

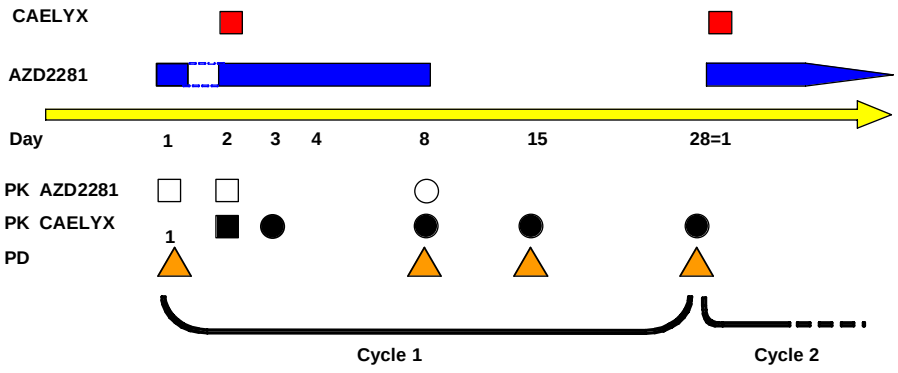
Figure 1 Concerted Escalation Design of AZD2281 and fixed dose of liposomal doxorubicin (40 mg/m^2)



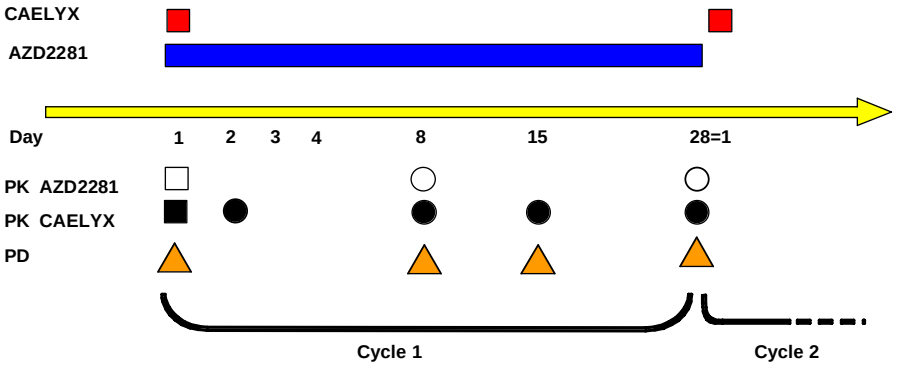
Expansion phase:
The 2 cohorts below MTD will be expanded to a maximum of 12 patients, to determine the recommended dose (RD). If MTD occurs at cohort 1, study is being closed, if MTD occurs at cohort 2, only cohort 1 will get expanded.

Figure 2 Schedules for Pharmacokinetic Evaluation

SCHEDULE 1: AZD2281 bid for 7 days out of 28-day schedule
CAELYX 40mg/m^2 1h-infusion every 4 weeks



SCHEDULE 2: AZD2281 bid continuously for 4 weeks
CAELYX 40mg/m^2 1h-infusion every 4 weeks



PK AZD2281 — 1 PK SAMPLE FOR AZD2281: Through level

PK DOXIL — 1 PK SAMPLE FOR DOXIL

PD: H2AX phosphorylation in PBMCs

PK AZD2281
Limited during the Dose Escalation Phase : 0, 1, 6, 10 hours post dosing
Full during the Expansion Phase at RD: 0, 0.5, 1, 2, 4, 6, 10 hours post dosing

PK DOXIL
0, 1 (end of infusion), 2, 6, 24, 168 (day8), 336 (day 15), 648 (day 28) hours

Figure 3 Study overview diagram

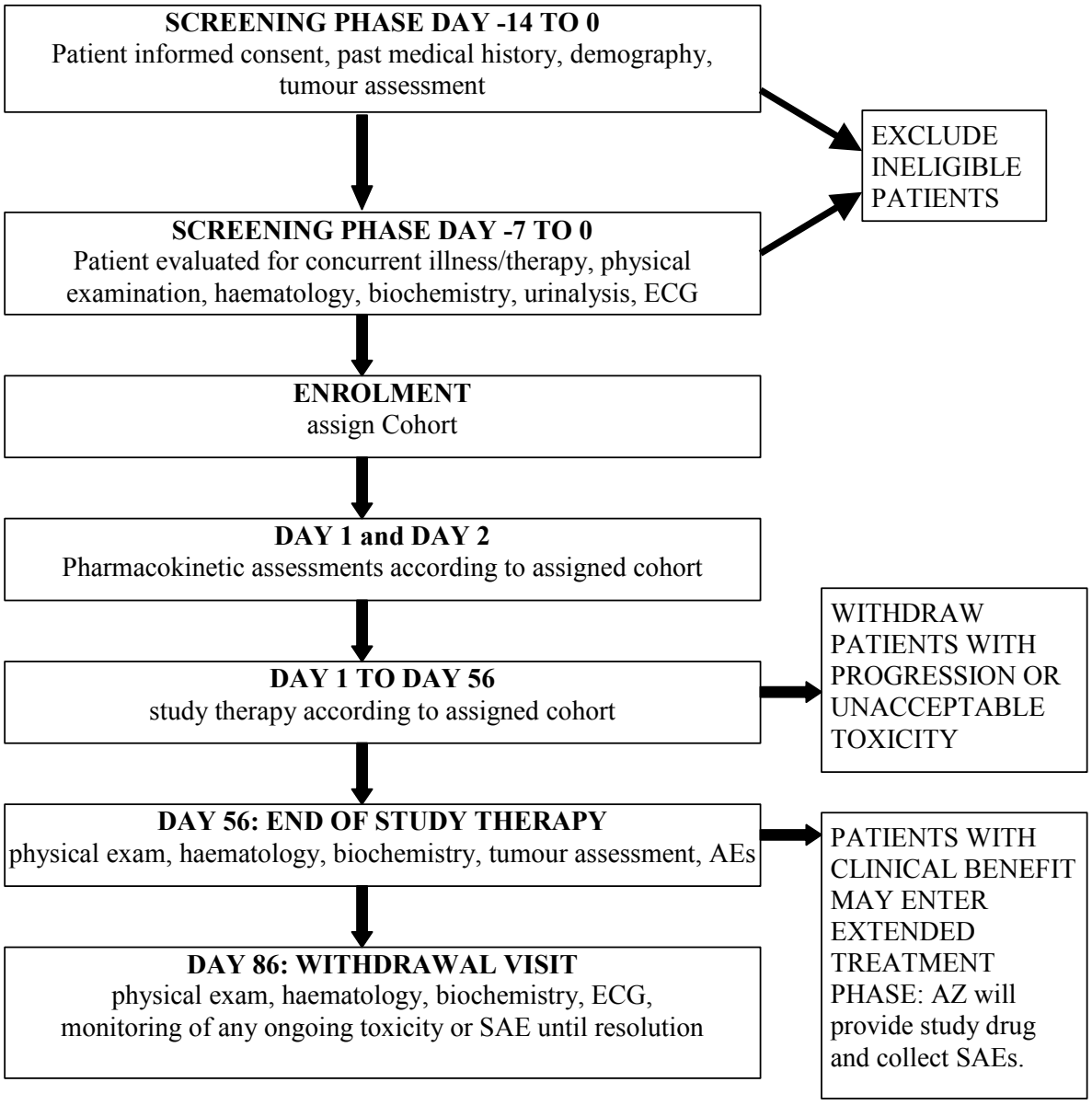


Table 1 Overall study plan

Screening Phase			**Standard Treatment Phase**										**end of study therapy**	**with-drawal**	**Extended treatment Phase**			
			cycle 1						**cycle 2**						**cycle 3**	**cycle 4**	**cycle 5**	**cycle 6**
Day	**-14 to 0**	**-7 to 0**	**1**	**2**	**3**	**8**	**15**	**28**	**29**	**36**	**43**	**50**	**56**	**86**	**57**	**85**	**113**	**141**
Visit number	**0**		**1**						**2**				**OF**	**ES**	**3**	**4**	**5**	**6**
Informed consent	x																	
Demography, med. history	x																	
ECOG PS and vital signs [a]		x	x			x	x		x		x		x	x	x	x	x	x
Physical examination		x	x			x	x		x		x		x	x	x	x	x	x
12-lead ECG	x							x					x	x		x		x
LVEF (by echography or MUGA)	x													x				x
Lab-haematology [a]		x	x[b]			x	x	x[c]			x		x[c]	x	x[c]	x[c]	x[c]	x[c]
Lab-biochemistry [a]		x	x[b]					x[c]					x[c]	x	x[c]	x[c]	x[c]	x[c]
Urinalysis + pregnancy test[d]		x												x				
CT or MRI	x[e]												x			day 112		day 168
PD blood sampling for H2AX			x			x	x	x										
PK blood sampling for AZD2281			PK	PK[f]		x		x[g]										
PK blood sampling for doxorubicin			PK[g]	PK[f] x[g]	x[f]	x	x	x										
Inclusion/exclusion criteria		x																
Administer Liposomal doxorubicin			x[g]	x[f]					x						Only patients with objective response after 2 cycles may continue with combination therapy [h,i].			

Screening Phase			Standard Treatment Phase										end of study therapy	with-drawal	Extended treatment Phase			
			cycle 1						cycle 2						cycle 3	cycle 4	cycle 5	cycle 6
Day	**-14 to 0**	**-7 to 0**	**1**	**2**	**3**	**8**	**15**	**28**	**29**	**36**	**43**	**50**	**56**	**86**	**57**	**85**	**113**	**141**
Visit number	**0**		**1**						**2**				**OF**	**ES**	**3**	**4**	**5**	**6**
Administer AZD2281 Cohort pilot, 1, 3, 5			one dose only	day 2-8 twice/ day					day 29-35						Patients with stable disease after 2 cycles may continue with AZD2281 monotherapy [h].			
Administer AZD2281 Cohort 2, 4, 6			continuous twice daily dosing															
Adverse events reviewing [k]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

a Laboratory/vital signs abnormalities should not be reported as AEs unless any criterion for a serious adverse event (SAE) is fulfilled, the laboratory/vital signs abnormality causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

b Lab-haematology and Lab-biochemistry need not be repeated on day 1, if screening values were within normal range.

c Lab-haematology and Lab-biochemistry samples may be collected within 72 hours before start of next cycle.

d Pre-menopausal women of child-bearing potential must have a negative urine or serum pregnancy test within 7 days before Day 1 of treatment. In the event of suspected pregnancy during the study, the test should be repeated. If the results are positive, the patient must be withdrawn immediately and AstraZeneca must be notified.

e CT or MRI baseline values may be performed within Day -21 to 0.

f Only patients in cohort: pilot, 1 ,3, 5. See Table 2 for details.

g Only patients in cohort 2, 4, 6. See Table 2 for details.

h Safety visits will be performed every 2 weeks until study drug discontinuation.

i A maximum of 6 cycles of lipsomal doxorubicin should be given. Further treatment is entirely at the discretion of the investigator.

k Adverse events must be collected from the time of informed consent, throughout the treatment period und up to and including 30 days post-study follow-up period. After discontinuation from treatment patients must be followed-up for any new adverse events for 30 calendar days. All SAEs must be reported within 24 hours. All AEs must be followed up until resolution unless in the opinion of the investigator the condition is unlikely to resolve due to the patient's underlying disease.

Table 2 Pharmacokinetics study plan

	AZD2281				Caelyx				
	DAY 1	**DAY 2**	**DAY 8**	**DAY 28**	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 8 DAY 15**	**DAY 28**
Cohorts pilot,									
1, 3, 5	0, 1, 6, 10*	0, 1, 6, 10*	x**	none	none	0, 1, 2, 6*	x**	x**	x**
- Dose escalation	0, 0.5, 1, 2, 4, 6, 10*	0, 0.5, 1, 2, 4, 6, 10*	x**	none	none	0, 1, 2, 6*	x**	x**	x**
- Expansion									
Cohorts 2, 4, 6									
- Dose escalation	0, 1, 6, 10*	none	x**	x**	0, 1, 2, 6*	x**	none	x**	x**
- Expansion	0, 0.5, 1, 2, 4, 6, 10*	none	x**	x**	0, 1, 2, 6*	x**	none	x**	x**

* hours post dosing
** collection of 1 blood sample

4. STOPPING CRITERIA FOR DOSE ESCALATION

3 patients will be dosed in each cohort initially (Figure 1):

- If no DLT within the first cycle, proceed to next dose level
- If 1 DLT, expand by 3 patients, if no further DLT, proceed to next dose level
- If ≥2 DLT in 6 patients, dose is considered not tolerable.

4.1 Dose limiting toxicity

Toxicity will be graded using the NCI common toxicity criteria for adverse events (NCI-CTCAE) version 3.0. DLT is defined as the following study drug related effects **AND** is considered related to the combination of AZD2281 and liposomal doxorubicin during cycle 1.

- Grade 4 Thrombocytopenia
- Grade 4 neutropenia lasting >5 days
- Grade 3/4 febrile neutropenia
- Grade 3 or greater nausea and/or vomiting despite maximal anti emetic therapy
- Other CTCAE grade 3 or higher non haematological toxicities

4.2 Rationale and risk/benefit assessment

4.2.1 Rationale for study design, doses and control groups

This study is designed to provide safety, tolerability and PK data for AZD2281 in combination with liposomal doxorubicin, in order to select an appropriate dosing regimen to potentially use in future Phase II efficacy studies. An open-label design is considered the most appropriate design for this purpose.

The dose levels of 100, 200 and 400 mg (twice daily) have been chosen, as previous Phase I studies have demonstrated that they are all generally well tolerated, yield systemic concentrations of AZD2281 likely to be biologically active. However, Swiss Health Authorities (Swissmedic) considered the starting dose of AZD2281 100 mg bid as too high, and the risk/benefit not to be in the patients best interest. Therefore, it has been decided to add a pilot phase, using a dose og 50 mg bid in combination with liposomal doxorubicin.

The number of patients required for the study has been based on the desire to obtain adequate tolerability, safety and PK data whilst exposing as few patients as possible to the study medication and procedures. In each cohort a minimum of 3 patients will receive AZD2281 in combination with liposomal doxorubicin. Cohorts may be expanded by 3 patients if 1 DLT is

seen. Therefore approximately 33 patients (21-54 depending on number of cohorts) may be enrolled into this study.

The design of concerted escalation of dose and dosing duration (Figure 2), by testing concomitantly the cohorts, could increase the speed of accrual by making available a higher number of free slots for accrual while preserving patient safety. This design has been already successfully applied by our institutions in a multicenter Phase I study coordinated by [redacted] (Sessa et al 2007).

A PK analysis will be performed which may enhance the understanding of the safety data, if any PK interactions are seen.

There is little data to suggest that a PK interaction will occur when AZD2281 is dosed in combination with liposomal doxorubicin. We believe with extensive monitoring for safety, administering AZD2281 at an initial dose of 50 mg (twice daily) in combination with the registered dose 40 mg/m^2 of liposomal doxorubicin every 28 days will be feasible.

The study population will be male or female patients with confirmed advanced metastatic solid tumors, not amenable to surgery or radiation therapy with curative intent.

4.3 Selection of study population

4.3.1 Study selection record

Investigator(s) must keep a record of subjects who were considered for enrolment but never enrolled eg, subject screening log, according to local procedures. This information is necessary to establish that the subject population was selected without bias.

4.3.2 Inclusion criteria

For inclusion in the study subjects must fulfil all of the following criteria:

1. Provision of written informed consent

2. Male or female aged 18 years or older

3. Histologically or cytologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent

4. Measurable or evaluable disease

5. ECOG Performance status 0 – 2 (see Appendix D)

6. Estimated life expectancy of at least 12 weeks

7. Negative pregnancy test for women of childbearing potential only (lack of childbearing potential is met by being post-menopausal, being surgical sterile, practicing contraception with an oral contraceptive or other hormonal therapy [eg,

hormone implants], intra-uterine device, diaphragm with spermicide or condom with spermicide, or being sexually inactive)

8. Adequate bone marrow, hepatic and renal function defined as:

   Haemoglobin ≥10.0 g/dL

   WBC >3 x 10^9 L

   Absolute neutrophil count ≥1.5 x 10^9 L

   Platelets ≥100 x 10^9 L

   Total bilirubin ≤1.5 x upper limit of normal (ULN)

   Aspartate transaminase (AST)(SGOT) and alanine transaminase (ALT)(SGPT) ≤2.5 x ULN (or ≤5 x ULN in the presence of liver metastases)

   Serum creatinine ≤1.5 x ULN

9. The patient is willing and able to comply with the protocol for the duration of the study period, including undergoing treatment and scheduled visits and examinations

4.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. More than 3 prior lines of chemotherapy for advanced disease

2. Less than 28 days from active treatment (ie, any treatment used to treat the disease) or high dose radiotherapy (patients may continue concomitant use of stable dose of bisphosphonates if used at least 28 days prior to commencing study treatment and patients may receive palliative radiotherapy for bone disease during the study)

3. Prior treatment with >300 mg/m^2 cumulative dose of doxorubicin equivalent

4. Resistance to anthracyclines defined as progressive disease during anthracycline treatment or within 6 months after the last anthracycline administration.

5. Symptomatic or known central nervous system tumors or metastases

6. Persistent CTC grade 2 or greater toxicities (excluding alopecia) caused by prior therapy

7. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, hepatic or renal disease, or any psychiatric disorder that prohibits obtaining informed consent

8. Presence of gastrointestinal disorders that, in the investigator's opinion, are likely to interfere with the absorption of AZD2281 or with the patient's ability to take regular oral medication

9. Patients known to be hypersensitive to liposomal doxorubicin, AZD2281or any excipients of the products

10. Patients with clinically significant cardiovascular disease or experienced clinically significant cardiovascular disease within the last 12 months

11. Patients requiring treatment with potent inhibitors or inducers of CYP3A4 (see Section 4.4.8.1 for guidelines)

12. Any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol.

13. Simultaneous participation in any other study involving an investigational medicinal product, or having participated in a study less than 28 days prior to the start of study treatment.

14. A positive pregnancy test. Pregnant or breast-feeding patient or patient of childbearing potential unless effective methods of contraception are used (lack of childbearing potential is met by being post-menopausal, being surgical sterile, practicing contraception with an oral contraceptive or other hormonal therapy [eg, hormone implants], intra-uterine device, diaphragm with spermicide or condom with spermicide, or being sexually inactive). Patients and their partners must agree to use one of the above forms of contraception throughout the treatment period and for 6 months after discontinuation of treatment.

15. Patients who are unable to swallow orally administered medication.

16. Patients who are immuno-compromised, eg, patients known to be serologically positive for human immunodeficiency virus (HIV).

17. Left ventricular ejection fraction below 50%

18. Major thoracic or abdominal surgery in 4 weeks prior to start of treatment

19. Previous treatment with AZD2281 or other drug with similar mode of action

4.3.4 Restrictions

Patients will be required to:

- Not donate blood during the study and for 3 months following their last dose of trial treatment.

- Concomitant use of known potent inhibitors or inducers of CYP3A4 (see Section 4.4.8.1).

- Patients should not take any additional medication without the prior consent of the investigator.

4.3.5 Discontinuation of subjects from treatment or assessment

4.3.5.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a subject from this study are:

- Voluntary discontinuation by the subject, who is at any time free to discontinue his/her participation in the study without prejudice to further treatment

- Safety reasons as judged by the investigator and/or AstraZeneca

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca.

- Incorrect enrolment ie, the subject does not meet the required inclusion/exclusion criteria for the study

- Subject lost to follow-up

- Disease progression

- Adverse event.

4.3.5.2 Procedures for discontinuation

Subjects who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). After discontinuation from treatment, patients must be followed up for all existing and new AEs for 30 calendar days (if SAEs, they must be reported to AstraZeneca within 24 hours) and followed until resolution unless, in the opinion of the Investigator, the condition is unlikely to resolve due to the patient's underlying disease. The patient should return all investigational products to the center.

4.4 Treatment(s)

4.4.1 Investigational product(s)

4.4.1.1 Identity of investigational product AZD2281

AZD2281 is a white to off-white crystalline solid with a molecular weight of 434 Da. The molecular formulation number is F013579.

Micronised AZD2281 will be supplied as an oral capsule, with Gelucire 44/14 (Lauroylmacrogylcerides) as excipients (solubiliser). Capsules will be Vcaps® Hydroxypropyl Methylcellulose Capsugel®. The capsules are not banded or enteric coated.

For this study, capsules are in one dosage strength: 50 mg, size 0, coloured white.

Table 3 Identity of investigational product

Investigational product	Dosage form and strength	Manufacturer	Formulation number	Batch number
AZD2281	50 mg	AstraZeneca	F013579	TBC

4.4.1.2 Identity of liposomal doxorubicin

Caelyx is provided in vials of 10 mL, containing 20 mg of doxorubicin hydrochloride in a pegylated liposomal formulation. 1 mL of Caelyx equals 2 mg liposomal doxorubicin hydrochloride.

4.4.1.3 Packaging/Labelling

AZD2281 will be supplied in High Density Polyethylene containers with a child-resistant cap. and will be dispensed to patients in the AstraZeneca packaging provided. Packaging includes bottles, caps and label.

The label will contain a tear off portion with space for the centre number and patient number to be completed and attached to the patient drug accountability paper case report form (pCRF) at the time of dispensing.

Commercial Caelyx® (liposomal doxorubicin) will be supplied by AstraZeneca and packaged and labelled in accordance with local regulations. Details of each dose administered and the duration of the infusion must be recorded in the CRFs .

4.4.1.4 Storage

All study drugs must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the AZD2281/Caelyx labels.

4.4.1.5 Accountability

The medication provided for this study is for use only as directed in the protocol. It is the investigator/institution's responsibility to establish a system for handling trial treatments, including investigational medicinal products, so as to ensure that:

- deliveries of such products from AstraZeneca are correctly received by a responsible person
- such deliveries are recorded

- study treatments are handled and stored safely and properly
- study treatments are only dispensed to study patients in accordance with the protocol
- any unused products are returned for destruction in liaison with their AstraZeneca monitor.

4.4.2 Doses and treatment regimens

Potentially up to 7 dose levels of AZD2281 will be explored in this study. In a pilot phase, 50mg twice daily for 1 week will be given, if MTD has not been reached, the main trial will be performed with 100 mg, 200 mg and 400 mg (twice daily for 1 week or continuous dosing) in order to confirm the dose levels that can be tolerated with liposomal doxorubicin. Patients with confirmed eligibility will be initially enrolled into cohort 1. At the end of the first cycle of the patients of each cohort, a safety review of the data will be performed.

Pilot Dose level (AZD2281 50 mg twice daily plus 40mg/m^2 Caelyx)

Three patients will be initially treated at AZD2281 doses of 50 mg bid:

One dose of 50 mg AZD2281 on day 1 followed by 50 mg twice daily on day 2-8 plus Caelyx 40 mg/m2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

- If no DLT within the first cycle, proceed to dose level of Cohort 1
- If 1 DLT within the first cycle, expand by 3 patients, if no further DLT, proceed to dose level of Cohort 1
- If ≥2 DLT within the first cycle in 6 patients, dose is considered not tolerable.

Cohort 1

One dose of 100 mg AZD2281 on day 1 followed by 100 mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 2

Continuous dosing of 100 mg AZD2281 twice daily plus Caelyx 40 mg/m2 on day 1 of a 28-day cycle.

Cohort 3

One dose of 200 mg AZD2281 on day 1 followed by 200 mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 4

Continuous dosing of 200 mg AZD2281 twice daily plus Caelyx 40 mg/m^2 on day 1 of a 28-day cycle.

Cohort 5

One dose of 400 mg AZD2281 on day 1 followed by 400 mg twice daily on day 2-8 plus Caelyx 40 mg/m^2 on day 2 of a 28-day cycle at cycle 1. From cycle 2 forward AZD2281 is given on day 1-7 and Caelyx is given on day 1.

Cohort 6

Continuous dosing of 400 mg AZD2281 twice daily plus Caelyx 40 mg/m^2 on day 1 of a 28-day cycle.

3 patients will be dosed in each cohort initially:

- If no DLT within the first cycle, proceed to next dose level
- If 1 DLT within the first cycle, expand by 3 patients, if no further DLT, proceed to next dose level
- If ≥2 DLT within the first cycle in 6 patients, dose is considered not tolerable.

Recommended dose: MTD will be considered to have been exceeded if ≥2 DLT in 6 patients occurred, and the two lower cohorts will then be expanded up to a maximum of 12 patients to confirm the recommended dose (RD). By choosing the 2 lower cohorts, they can then be compared in terms of toxicity and biological effects (pharmacodynamic marker). It could be that the higher dose for a shorter period is as effective as the lower dose given continuously and it is better tolerated or vice versa.

The doses of AZD2281 will be made up from 50 mg capsules to be taken orally twice daily. Patients should swallow the medication whole with a glass of water in the morning and in the evening at the same time each day. This is to ensure approximately a 12-hour interval between doses. On days that PK samples will be taken, patients are allowed to have a light meal up to one hour before their dose and must refrain from eating for at least 2 hours after each dose.

4.4.2.1 Management of toxicity due to AZD2281

Any toxicity CTC grade 3-4 observed during the course of the study will be managed by interruption of the dose for a maximum of 28 days. AZD2281 must be interrupted until the patient recovers completely or the toxicity reverts to NCI-CTCAE grade 1 or less.

Where toxicity recurs following re-challenge with AZD2281, then the patient is to be considered for dose reduction or withdrawal.

Table 4 Dose reductions for AZD2281 due to NCI-CTCAE grade 3 or 4 treatment-related SAEs/AEs

Initial Dose Level	1st Dose Reduction	2nd Dose Reduction
50 mg bid	No reduction allowed – withdraw patient.	
100 mg bid	50 mg bid	Not applicable.
200 mg bid	100 mg bid	50 mg bid
400 mg bid	200 mg bid	100 mg bid

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of AZD2281. If this has not resolved to at least NCI-CTCAE grade 1 or less during the maximum 28-day period, and/or the patient has undergone the permissible number of dose reductions already, the patient is to be withdrawn. If toxicity is appropriately resolved, then the patient should restart treatment with AZD2281 but with a 50% dose reduction. If the event recurs with the same severity, treatment should be interrupted again and, on resolution, a further dose reduction made if permissible (see Table 4). If, on re-starting treatment, the event continues to occur, treatment should be stopped and the patient withdrawn. A maximum of 2 dose reductions of 50% is possible depending on the dose cohort level providing the dose of AZD2281 does not fall below 50 mg bid.

For other toxicities, CTCAE grade 3, investigators should use their discretion in deciding whether interruptions are necessary and should also treat the events as medically appropriate based on the signs and symptoms.

The dose of AZD2281 must not be adjusted under any other circumstances unless prior agreement is given by AstraZeneca. All dose modifications and interruptions (including any missed doses), and the reasons for the modifications/interruptions are to be recorded in the CRF.

For surgery, up to 21-days drug interruption is allowed. AZD2281 should be stopped 3 days before surgery and re started approximately 10 days later. If the wound has not healed well, a further 7 days may be allowed and the patient recommence AZD2281 if there is no evidence of disease progression. No dose interruption of AZD2281 is required for any biopsy procedures.

4.4.2.2 Management of toxicity due to liposomal doxorubicin (Caelyx)

The following information is based on Caelyx SmPC. Please refer to your local core data sheet for clarification if necessary. Treatment with Caelyx should be postponed until recovery of toxicity and the dose for retreatment should be decreased according to Table 5and Table 6.

Table 5 **Dose reductions for Caelyx in case of Palmar-Plantar Erythrodysesthesia (PPE) or stomatitis at week 4**

NCI-CTCAE	week 4	week 5	week 6
Grade 1	**Redose, unless** patient had previously a similar grade 3/4 tox, in which case wait an additional week.	**Redose, unless** patient had previously a similar grade 3/4 tox, in which case wait an additional week.	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment.
Grade 2	Wait an additional week	Wait an additional week	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment.
Grade 3	Wait an additional week.	Wait an additional week.	**Withdraw patient.**
Grade 4	Wait an additional week.	Wait an additional week.	**Withdraw patient.**

Table 6 **Dose reductions for Caelyx in case of haematological toxicity (neutrophils or platelets) at week 4**

NCI-CTCAE	Neutrophils (ANC)	Platelets	Modification
Grade 1	1,500 - 1,900	75,000 - 150,000	Resume treatment with no dose reduction.
Grade 2	1,000 - <1,500	50,000 - <75,000	Wait for a maximum of 2 weeks until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction
Grade 3	500 - <1,000	25,000 - <50,000	Wait for a maximum of 2 weeks until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
Grade 4	<500	<25,000	Wait for a maximum of 2 weeks until ANC ≥1,500 and platelets ≥75,000; decrease dose by 25%

Patients with impaired hepatic function

It is recommended that the liposomal doxorubicin dosage be reduced if the bilirubin is elevated in either of the following 2 categories:

Serum bilirubin 1.2 – 3.0 mg/dL.

Serum bilirubin >3.0 mg/dL.

For further guidance, please refer to the local core data sheet.

Cardiac Toxicity

Special attention must be given to the risk of myocardial damage from cumulative doses of liposomal doxorubicin. Cardiac function should be carefully monitored using echocardiography or other suitable methods during liposomal doxorubicin therapy (see Table 5) Echocardiography/ MUGA scans should be performed at baseline and at withdrawal. Furthermore, when the cumulative anthracycline dose is ≥300 mg/m2 (based on doxorubicin), echocardiography or MUGA scan should be performed every other cycle, together with ECG. If the patient's left ventricular ejection fraction is decreased by >20% from baseline or is less than 45%, the patient should be considered for withdrawal from the study. The total dose should not exceed lifetime cumulative dosing as per local/pharmacy guidelines. ECGs should also be performed at baseline and at withdrawal (see Table 5).

Infusion related reactions

The initial rate of infusion of liposomal doxorubicin should be 1 mg/min to help minimise the risk of infusion related reactions. Medications to treat such infusion related reactions as well as emergency equipment should be available.

Precautions should be taken to avoid extravasation reactions with iv administration of liposomal doxorubicin. If any signs or symptoms of extravasation occur, the infusion should be immediately terminated and restarted in another vein. Application of ice over the site for approximately 30 minutes may be helpful in alleviating the local reaction.

4.4.2.3 Management of toxicity attributable either to AZD2281 or Caelyx

Caelyx should be given with AZD2281; in case Caelyx cannot be re-dosed on day 29 (because of PPE for example), AZD2281 is continued if it is given continuously (cohorts 2, 4, 6) but it cannot be restarted if given intermittently (cohorts pilot, 1, 3, 5); in this case, AZD2281 should be restarted at the same time of Caelyx. If Caelyx cannot be continued because of toxicity, the continuation of treatment with single agent AZD2281 is to be discussed with the chairperson of the study and the Sponsor.

4.4.3 Method of assigning subjects to treatment groups

Before a center screens a patient, a filled-in pre-registration form needs **to be faxed to the allocation office at** [redacted] The allocation office will assign a unique patient number (UPN) and block a place in the currently open cohort. The UPN consists of a 7-digit number, e.g. E1010001. The first 3 digits being the centre number, the middle digit the cohort number (e.g. 0 for pilot cohort, 1 for cohort 1, 2 for cohort 2 and so on) and the last 3 digits represent the number of the next subject entering screening. Patients will be entered strictly sequentially as they become

eligible for screening. Patient numbers will begin at 001 and will be allocated sequentially across all study centres. Patients will be entered into the cohort that is recruiting at the time of enrolment, until there are sufficient patients in that cohort. If a subject is not eligible for enrolment or discontinues from the study, the subject E-code will not be re-used, and the subject will not be allowed to re-enter the study.

After completion of the pilot cohort, a design of concerted escalation of dose and dosing duration will be applied according to which the shorter schedule (7 day-dosing) is tested first; if proven tolerable, the tolerability of the same dose given for 4 weeks is assessed while the tolerability of a higher dose given for 7 days is assessed concomitantly (Figure 2). According to this design, the 1-week schedule, potentially more toxic but also more easily monitored, is driving the dose schedule. This design could increase the accrual of patients and could shorten the duration of the study, while preserving patient safety (Sessa et al 2007) (Figure 2).

Written informed consent will then be obtained before screening of a patient. Patient's eligibility will be confirmed by fax to the allocation office and the cohort will be allocated in return.

4.4.4 Blinding and procedures for unblinding the study (Not applicable)

This is an open labelled study design, therefore blinding is not applicable.

4.4.5 Concomitant medication

Any medications, with the exceptions noted in Section 4.4.8 below, which are considered necessary for the patient's welfare, and which it is believed will not interfere with the study medication, may be given at the discretion of the Investigator, providing the medications, the doses, dates and reasons for administration are recorded in the CRF.

In addition, any unplanned diagnostic, therapeutic or surgical procedure performed during the study period must be recorded in the comments section of the corresponding Adverse Event report.

Between study visits, in order to verify dosing compliance and times of administration of AZD2281, patients will be asked to complete details of any self-medication in a diary card, and during the study visits special attention will be paid to questioning patients in relation to any self-medication.

Prophylactic anti-emetics and/or anti-diarrhoeals for counteracting the toxicity of AZD2281 or liposomal doxorubicin can be given. Should a patient develop nausea, vomiting and/or diarrhoea which, in the Investigator's opinion, is considered to be related to the study drugs, then appropriate prophylactic treatment may be given.

Prophylaxis with granulocyte colony stimulating factor (G-CSF)/granulocyte macrophage colony-stimulating factor (GM-CSF) and erythropoietin is prohibited during the first cycle of therapy. It should only be used during the study after a relevant AE has occurred. In this case, their use is permitted at the Investigator's discretion and according to local hospital guidelines.

However, if the patient has an ANC (absolute neutrophil count) <500 for longer than 5 days or fails to recover to the required neutrophil count within 14 days or has febrile neutropenia, then the use of G-CSF or GM-CSF is permitted in accordance with local clinical practice. The reason(s) for the use, doses and dates of treatment should be recorded in the patient's medical records and appropriate section of the CRF.

Planned major surgery should not be carried out within 4 weeks of last iv infusion of Caelyx.

4.4.6 Palliative radiotherapy

Palliative radiotherapy may be used for treatment of pain at the site of bony metastases that were present at baseline providing the investigator does not feel that these are indicative of clinical disease progression during the study period.

4.4.7 Administration of other anti-cancer agents

Patients must not receive any concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates for bone disease, and non-suppressive doses of corticosteroids provided the dose is stable before and during the study.

4.4.8 Medications that may NOT be administered

No other chemotherapy, immunotherapy, hormonal therapy or other novel agent is to be permitted during the course of the study for any patient.

Prophylactic cytokine administration should not be given in the first cycle.

An increased risk of infection by the administration of live virus and bacterial vaccines have been observed with conventional doxorubicin. Effects with AZD2281 are unknown and therefore they should not be administered to patients in any treatment group.

4.4.8.1 Inducers of CYP3A4

The use of any herbal/natural products or other "folk remedies" should be discouraged, but use of these products, as well as the use of vitamins, nutritional supplements, and all other concomitant medications must be recorded in the CRF.

AZD2281 is an investigational drug, for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data AZD2281 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of AZD2281 is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving AZD2281.

Whilst this is not an exhaustive list, it covers the known potent inhibitors who have most often previously been reported to be associated with clinically significant drug interactions:

- Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers are excluded:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone and St John's Wort (wash-out period for phenobarbitone 5 weeks and for any of the others 3 weeks).

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Medical Advisor, and a decision to allow the patient to remain on study will be made on a case-by-case basis.

4.4.8.2 Liposomal doxorubicin

No formal drug interaction studies have been conducted with liposomal doxorubicin. However, it may interact with drugs known to interact with the conventional formulation of doxorubicin HCl.

4.4.9 Treatment compliance

Doses of Caelyx will be administered in the clinic as per normal clinical practice. Each patient will be given a diary card to complete throughout the study. This card will contain the AZD2281 dose level the patient has been assigned to, how many tablets should be taken each day and how the tablets should be stored. Patients will be asked to record the date and time of each dose of AZD2281 they take.

A member of the Investigator site study team will query the patient for treatment compliance at each visit. All patients must return their bottle(s) of AZD2281 at the appropriate scheduled visit, when a new bottle will be dispensed. An assessment of compliance (capsule count) of any remaining capsules in the bottle(s) will be performed in order to determine if the patient is following their treatment dose schedule. Compliance will be assessed by the capsule count and the information will be recorded in the appropriate section of the CRF. After the capsule count has been performed, the remaining capsules will not be returned to the patient but will be retained by the Investigative site until reconciliation is completed by the study monitor.

5. MEASUREMENT OF STUDY VARIABLES

A patient will be defined as evaluable for assessment of safety of AZD2281 in combination with liposomal doxorubicin if they received at least one dose of either agent.

A patient will be defined as evaluable for assessment of efficacy of AZD2281 in combination with liposomal doxorubicin if they complete at least 1 cycle of liposomal doxorubicin (28 days) and also receive at least 75% of the planned dosing of AZD2281 during this cycle.

Patients are evaluable for PK evaluation if they are able to provide a full AZD2281 PK profile.

A schedule for the tests and evaluations to be conducted in the study are presented in Table 1 and Table 2.

5.1 Medical examination and demographic measurements

5.1.1 Enrolment medical examination and demographic measurements

Each subject will undergo an enrolment medical examination in the 7 days prior to the first study visit. This will consist of:

- Recording of demographic data - date of birth, sex, height, weight, race.
- A standard medical/surgical history and a physical examination including the cardiovascular and respiratory systems.
- ECOG performance status.
- A blood sample for standard clinical chemistry and haematology assessments and a mid-stream urine sample for urinalysis.
- A resting blood pressure and pulse rate measurement.
- Recording of a 12-lead ECG.
- Measurement of LVEF by echocardiography or MUGA-scan.
- Recording of prior anticancer therapy and all concomitant medication.
- Adverse events.

5.1.2 Physical examination

Physical examination will include the assessment of the body systems listed below and reporting if these findings were normal, abnormal or not done. If any abnormal findings are reported, the abnormality must be specified. The following must be assessed:

- General appearance
- Ears, eyes, nose and throat
- Cardiovascular

- Respiratory
- Gastrointestinal
- Genitourinary
- Endocrine
- Central Nervous System
- Dermatological
- Musculoskeletal
- Peripheral lymph nodes
- Other.

5.1.3 Body weight

Body weight will be measured in kilograms (kg) using a standard scale. Patients should be weighed while wearing light indoor clothing without any footwear. Efforts should be made to use the same scales for each assessment to minimise equipment variability.

5.1.4 Performance status (ECOG)

The patient's ECOG performance status will be assessed (see Appendix D).

5.1.5 Post-study medical examination

Where possible, a follow-up medical examination should be performed approximately 30 days after the last dose of AZD2281. This will include a 12-lead ECG, measurement of LVEF, a review of AEs and of concomitant medication. Clinical chemistry, haematology and urinalysis will be assessed.

5.2 Pharmacokinetic measurements

For timing of individual samples refer to the study plan (Table 1 and Table 2).

5.2.1 Determination of drug concentration in biological samples

Samples for measurement of doxorubicin concentration will be analysed by [redacted] Samples for measurement of AZD2281 will be analysed by [redacted] The methods used will be referred to in the clinical study report.

5.2.2 Collection of biological samples

Blood samples (4 mL) for determination of AZD2281 and doxorubicin in plasma will be taken at the times presented in the study plan (Table 2). Plasma will be separated, labelled and

shipped as detailed in Appendix C. The date and time of collection will be recorded on the appropriate CRF. Samples should be stored at -20 °C (-80 °C for Caelyx determination) and analysed within the timeframe after collection for which the stability in the samples has been validated and found acceptable (12 months for AZD2281 and 6 months for doxorubicin). Results from samples stored longer than the period stated will not be reported.

Samples will be disposed of after the clinical study report has been finalised.

5.3 Pharmacodynamic measurements

Blood samples (8 mL) for determination of histone H2AX phosphorylation in PBMCs will be taken at the times presented in the study plan (Table 1). Blood samples will be collected in Cell Preparation Tubes (VACUTAINER CPT, Becton Dickinson, Franklin Lakes, NJ), PBMC will be isolated, labelled and shipped as detailed in Appendix C. The date and time of collection will be recorded on the appropriate CRF.

Histone H2AX phosphorylation in PBMCs will be analysed by Flow Cytometry method for intracellular staining using an anti-phospho-H2AX (Ser139) antibody.

5.4 Safety measurements

5.4.1 Laboratory safety measurements

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis parameters will be taken at the times given in the study plan (Table 1). The date of collection will be recorded on the appropriate CRF.

The following laboratory assessments will be measured:

Table 7 Laboratory safety assessments

Clinical chemistry	Haematology	Urinalysis
Calcium	Haemoglobin	Blood
Sodium	Red blood cell count (RBC)	Glucose
Potassium	Platelet count	Protein
Magnesium	White blood cells	
Chlor	Differential white cell count	
Glucose	Absolute neutrophil count (ANC)	
Creatinine	Activated partial thromboplastin time (APTT)	
Total bilirubin	International normalised ratio (INR)	
Urea	MCV (Mean Corpuscular Volume)	
Alkaline phosphatase (ALP)	MCH (Mean Corpuscular Hemoglobin)	
Asparate transaminase (AST)	MCHC (Mean Corpuscular Hemoglobin Concentration)	

Clinical chemistry	Haematology	Urinalysis
Alanine transaminase (ALT)		
γ-Glutamyl-transpeptidase (GGT)		
Total protein		
Albumin		
Lactic dehydrogenase (LDH)		
Lipase		
Amylase		

5.4.2 Other samples

5.4.2.1 Serum or urine pregnancy test

Pregnancy tests on blood or urine samples will be performed for pre menopausal women of childbearing potential at screening. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be withdrawn from the study. In the event of a suspected pregnancy during the study, the test should be repeated.

5.4.2.2 Urinalysis

Urinalysis will be performed using a dipstick for blood and protein. Other abnormal results should be collected if appropriate. Microscopic analysis will be performed by the hospital's local laboratory if clinically indicated.

5.4.3 Electrocardiographic measurements

For timing of individual measurements refer to study plan (Table 1).

5.4.3.1 Resting 12-lead ECG

Twelve-lead ECGs will be obtained after the subject has been lying down for 5 minutes in each case. ECGs will be recorded at 25 mm/sec. ECG data will be recorded on the appropriate CRF. At each time point 2 identical ECG copies will be taken (one for AstraZeneca, one to be retained by the site).

The investigator or designated physician will review the paper copies of each 12 lead ECG and provide an overall clinical assessment. If there is a clinically significant abnormal finding this should be reported as an adverse event.

5.4.4 Vital signs

5.4.4.1 Blood pressure and pulse

For timing of individual measurements refer to study plan (Table 1).

5.4.5 Subjective symptomatology

Symptoms reported spontaneously by the patient will be recorded throughout the study period. Symptoms reported will be reviewed by the Investigator and recorded as adverse events on the patient's CRF if appropriate. Patients will be assessed for the presence of adverse events from time of consent, throughout the treatment period, and up to and including the 30-day follow-up period after the last administration of the study medication. Adverse events will be graded according to the National Cancer Institute Common Terminology (NCI CTC) Criteria version 3.0 for cancer clinical trials (CTCAE).

5.5 Genetic measurements and co-variables (Not applicable)

No genetic measurements will be done.

5.6 Volume of blood sampling

The total volume of blood that will be drawn from each subject in this study is as follows:Table 8 Volume of blood to be drawn from each subject completing 2 cycles of study treatment

Assessment		**Sample volume (mL)**	**n of samples[a]**	**Total volume (mL)**
Pharmacokinetic		4	14-23	56-92
Pharmacodynamics		8	4	32
Safety	Clinical chemistry	6[b]	5	30
	Haematology	9[b]	8	72
Total				**190 - 226 mL**

a Depending of cohort allocation and does escalation or expansion phase
b These are approximate volumes that are subject to site specific changes

5.7 Adverse Events

The methods for collecting adverse events are described below.

5.7.1 Adverse Events

5.7.1.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product,

whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by any of the following – study medication – other medication?". For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other Significant Adverse Events (OAE)

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Patient Safety Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these may be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

5.7.1.2 Time period for recording of adverse events/SAEs

Non serious AEs and SAEs will be collected from the time consent is given throughout the treatment period and up to and including the 30-day follow-up period.

In addition, any known untoward event occurring subsequent to the AE reporting period that the investigator assesses as possibly related to the study medication(s) should also be reported as an AE.

5.7.1.3 Eliciting AEs/SAEs

At each visit the method of detecting AEs and SAEs in this study will be by the following:

- Information volunteered by the patient, or carer.
- Open-ended and non-leading verbal questioning of the patient at every visit such as the following: How are you feeling? Do you have any health problems? Have you had any (other) medical problems since your last visit?
- Observation by the investigational team, other care providers or relatives.

5.7.2 Definition of relationship of AEs to the study medication

The Investigator will also be asked to assess the possible relationship between the AE and the study medication. For an AE to be a suspected drug-related event, there should be at least a reasonable possibility of a causal relationship between the study medication and the AE. Expectedness will be based on a review of the Investigator Brochure.

- Time course – temporal relationship to receiving drug,
- Consistency with known drug profile,
- De-challenge experience – AE resolves after stopping drug,
- No alternative cause – AE cannot be explained by aetiology, underlying disease, etc,
- Re-challenge experience – AE reoccurs when drug reintroduced,
- Laboratory tests.

The causality of AEs (ie, their relationship to study treatment) will be assessed by the Investigator(s) who in completing the relevant CRF must answer 'Yes' or 'No' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by any of the following-study medications (AZD2281, doxorubicin) -other medication?'.

For further guidance on the interpretation of the causality question see Appendix B of the protocol.

In addition to making a causality assessment with respect to the study treatment, the Investigator should also consider whether study participation (ie, protocol mandated procedures such as invasive tests, change to existing therapy) contributed to the occurrence of the event. SAEs considered to be related to study participation, should be reported in the usual SAE timeframes to AZ whether they occur pre-, during or post- the study treatment period.

5.7.3 Definition of severity of AEs

The severity of any AE will be graded according to the NCI-CTCAE, version 3, where applicable.

For each episode, the highest severity grade attained should be reported.

If an AE occurs that is not listed in the NCI-CTCAE booklet, the Investigator will evaluate its severity using the definitions in the table below.

Table 9 Definition of severity of adverse events

Severity	Description
Mild	Grade 1 – Does not interfere with the patient's usual function (awareness of symptoms or signs, but easily tolerated (acceptable)).
Moderate	Grade 2 – Interferes to some extent with the patient's usual function (enough discomfort to interfere with the usual activity (disturbing)).
Severe	Grade 3 – Interferes significantly with the patient's usual function (incapacity to work or to do usual activities (unacceptable).
Life-threatening	Grade 4 – Results in risk of death, organ damage or permanent disability (unacceptable)
Death	Grade 5 – Event has a fatal outcome

Note the distinction between the seriousness and the intensity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 5.7.1.1.

5.7.4 Study-specific considerations regarding definitions of AEs/SAEs

5.7.4.1 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the type of cancer for which the study medications are being studied. It may be an increase in the severity of the cancer or an increase in the symptoms of the cancer. Expected progression of the patient's cancer and /or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition,

should not be reported as an AE. Any events that are unequivocally due to progression of disease must not be reported as an AE.

The development of new metastases, or progression of existing metastases to the primary cancer under study, should be considered as disease progression and not an AE. Signs and symptoms clearly associated with metastases present at study entry should not be reported as AEs unless they are newly emergent (ie, not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease related signs and symptoms to be caused directly by the study medication.

5.7.4.2 Abnormal laboratory findings/vital signs

The reporting of laboratory findings/vital sign abnormalities as both laboratory findings/vital signs and AEs should be avoided. They should not be reported as an AE unless: any criterion for an SAE is fulfilled, the laboratory finding/vital sign abnormalities causes the patient to discontinue from the study, or the investigator insists the abnormality should be reported as an AE. If an abnormal laboratory finding/vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory finding/vital sign should be considered additional information that must be collected on the relevant CRF.

5.7.4.3 Lack of efficacy

When there is deterioration in the condition for which the study treatment(s) is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

5.7.4.4 Deaths

All deaths that occur during the study, or within the protocol-defined 30-day post-study follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the CRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the study monitor as a SAE within 24 hours (see Section 5.7 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information can be captured in the ‘death CRF’.

- Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety Department within the usual timeframes.

5.7.4.5 New cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 5.7). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

5.7.4.6 Overdose

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, regardless of whether the overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

5.7.4.7 Pregnancy

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4 Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

5.7.4.8 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Patient Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above.

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the Case Report Form. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. For studies in countries

implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (see Section 8.2).

5.8 Follow-up of adverse events/serious adverse events

After the initial AE/SAE report, the Investigator is required to follow-up proactively each patient and provide further information to AZ on the patient's condition. All AEs / SAEs should be followed up to resolution, or until the condition stabilises, unless the event is considered by the Investigator to be unlikely to resolve due to the patient's underlying disease, or the patient is lost to follow-up. The Investigator must also report follow-up information on SAEs within the same timeframes. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AZ within 24 hours as described in Section 5.7.4.8 above.

For SAEs, follow-up reports (as many as required) should be completed and faxed/emailed following the same procedure as above.

A final report is required for SAEs once the condition is resolved or stabilised and no more information about the event is expected. The final report should be completed and faxed/emailed following the same procedure as above.

5.9 Handling unresolved adverse events/serious adverse events at withdrawal

All AEs and SAEs must be followed until resolution, unless, in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease or the patient is lost to follow-up.

The sponsor reserves the right to ask for further information on any AE which may be considered of interest.

6. STUDY MANAGEMENT

6.1 Monitoring

6.1.1 Study monitoring

The monitoring of this study will be performed in accordance with the principles of Good Clinical Practice (GCP) as laid out in the International Conference on Harmonisation (ICH) document "Good Clinical Practice: Consolidated Guideline".

6.1.2 Data verification

It is a prerequisite of this study that the study monitor has direct access to source data for data verification. This will be done by comparing data from the CRFs with those in the subject's medical notes (permission from the subject will be sought as part of the consent process).

Such verification is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

For this study original data recorded on the CRF and regarded as source data are as follows:

- Actual date and time of dosing on the days of PK blood sampling.
- Actual date and time of collection of PK blood samples.

Monitoring including source data verification should routinely be performed prior to the transfer of data to Data Management.

6.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, GCP guidelines of the ICH and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her centre.

6.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

6.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the principal investigator and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol must be notified to or approved by each Ethics Committee, and in many countries also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a protocol amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Master Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s).

6.5 Study agreements

The principal investigator at each centre must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this protocol shall prevail.

6.6 Study timetable and end of study

The study is expected to start in December 2008 and to be completed by March 2010.

The end of the study will be declared once all enrolled patients complete study medication or a programme has been established for remaining patients still receiving study treatment after the final analysis has been performed.

6.7 Data management

6.7.1 Case report forms

Electronic CRFs (eCRFs) will be used to record all data. Data from the completed eCRFs will be entered onto [redacted] clinical study database and validated under the direction of the Data Manager. Any missing, impossible or inconsistent recordings in the eCRFs will be referred back to the Investigator using a data query form and be documented for each individual subject before clean file status is declared.

The principal investigator/sub-investigator will record data on the observations, tests and assessments specified in the protocol on the eCRFs provided by [redacted] The CRF will be accompanied with 'instructions for the Investigator', which should be followed. These instructions will provide guidance for the recording of the study data in the CRF including how to change data incorrectly recorded. These instructions are an important part of quality control and standardisation across the study. Quality control procedures will be applied to each stage of the data handling to ensure that all data are reliable and have been processed correctly.

7. PHARMACOKINETIC, PHARMACODYNAMIC, SAFETY, GENETIC AND STATISTICAL METHODOLOGY

7.1 Pharmacokinetic / pharmacodynamic evaluation

7.1.1 Calculation or derivation of pharmacokinetic variables

Samples for measurement of doxorubicin concentration will be analysed by [redacted] For Caelyx, C_{max}, t_{max}, $AUC_{0\text{-infinity}}$, V_{ss} and ClTB of total doxorubicin released from liposome by Triton X-100 will be assessed.

Samples for measurement of AZD2281 will be analysed by [redacted] For AZD2281, C_{max}, t_{max}, AUC_{0-10} and C_{min} will be calculated.

All plasma concentration-time data will be analysed using non-compartmental methods.

C_{max}, C_{min} and t_{max} for AZD2281 and doxorubicin respectively will be calculated for each patient directly from their plasma concentration-time profiles, and AUC will be calculated by the linear trapezoidal rule.

An assessment of any marked change in AZD2281 exposure when dosed alone or together with Caelyx will be made for data collected from Schedule 1. PK variables derived from a single dose of AZD2281 given on day 1 of cycle 1 will be compared with that calculated on day 2, when the single dose will be administered contemporaneously with Caelyx. This will allow an intra-patient comparison of AZD2281 exposure. A Student's t-test for paired data (two-tailed) will be used to determine statistically significant differences.

For Caelyx only an inter-patient comparison will be done to clarify any dose-dependent or schedule-dependent PK interference.

All pharmacokinetic variables will be summarized and listed.

7.2 Safety evaluation

7.2.1 Calculation or derivation of safety variables

Safety and tolerability data will be assessed in terms of AEs, laboratory data and vital sign data that will be collected for all patients. Safety data will be presented according to dose AZD2281 received. Appropriate summaries of these data will be presented.

7.3 Statistical methods and determination of sample size

7.3.1 Statistical evaluation

All statistical analyses will be the responsibility of [redacted] A Statistical analysis plan (SAP) will be produced prior to database lock.

7.3.2 Description of variables in relation to hypothesis

The primary objective of this study is to assess the recommended dose of AZD2281 when given in combination with liposomal doxorubicin in patients with advanced solid tumors. The assessment will be based on adverse events, vital signs including blood pressure (BP) and pulse rate (PR), ECG, haematology, clinical chemistry, urinalysis and physical examination.

7.3.3 Description of analysis sets

All patients that receive a dose of study medication will be included in the assessment of safety and tolerability.

Patients will be included in the PK analysis providing they have had a full PK profile for AZD2281. All PK data will be retained for use in the summaries and listings.

7.3.4 Methods of statistical analyses

There will be no formal statistical analysis of safety and tolerability data.

All AEs will be listed for each patient and summarised by body system and preferred term assigned to the event using the MedDRA dictionary. All clinical chemistry, haematology, urinalysis, vital signs (PR and BP) and ECG data will be summarised and listed.

There will be no formal statistical analysis of the PK variables. All pharmacokinetic variables will be summarised and listed.

7.3.5 Determination of sample size

The number of patients has been based on the desire to obtain adequate tolerability, safety, and pharmacokinetic data whilst exposing as few subjects as possible to the study medication and procedures. In each cohort, the safety review will be performed on a minimum of 3 and a maximum of 6 evaluable patients. A maximum of 12 patients will be treated in the expanded cohorts determined for the evaluation of RD.

7.4 Interim analyses (Not applicable)

No interim analyses will be performed.

7.5 Data presentation

Details of the data presentation will be provided in the SAP.

7.6 Safety monitoring committee

Following completion of recruitment of patients into a cohort, a safety review committee will be set up to review the safety data for that cohort. The committee will comprise of an Investigator (or delegate from each centre), AZ physician, [redacted]statistician (or nominated deputy in each case). The committee must comprise of a minimum of 2 physicians but may also include other members of the study team.

8. ETHICS

8.1 Ethics review

AstraZeneca will provide Ethics Committees and Principal Investigators at each site with safety updates/reports according to local requirements.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate.

The investigator must submit written approval to AstraZeneca before he or she can enrol any subject into the study.

The Principal Investigator at each site is responsible for informing his/her Ethics Committee of any amendment to the protocol in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the Ethics Committee annually, as local regulations require.

8.2 Reporting serious adverse events to IEC/IRB and competent authorities

In addition to reporting the SAE to AZ, the Investigator must also comply with the applicable requirements related to the reporting of SAEs to the Independent Ethics Committee (IEC) which approved the study. The Investigator must promptly report all deaths to the IEC which approved the study.

The Sponsor is responsible for informing the Regulatory Authority of SAEs/SUSARs as per the European (EU) Clinical Trials Directive and/or local country regulations and guidelines. AstraZeneca will be responsible for safety regulatory reporting.

In compliance with the European Clinical Trials Directive and/or local country requirements, AstraZeneca will provide Ethics Committees, Investigators and Regulatory Authorities with periodic safety update reports of all SAEs (SSARs and/or SUSARs) attributed to the use of AZD2281 which are reported to the Sponsor.

Copies of all correspondence relating to reporting of any SAEs to the IEC should be maintained in the Investigator's File and provided to AZ.

8.3 Ethical conduct of the study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.4 Informed Consent

The principal investigator at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Informed Consent Form. A copy of the Informed Consent Form must be given to the subject.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.5 Subject data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by an enrolment code/study randomisation code and initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact AstraZeneca personnel shown below.

Please call the number above and ask the security to page the physician on call for AZD2281.

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. A medical emergency usually constitutes an SAE and should be reported as such, see Section 5.7.4.8.

9.3 Procedures in case of overdose

There is no specific treatment in the event of overdose of AZD2281 and possible symptoms of overdose are not established. Adverse reactions associated with overdose should be treated symptomatically, and should be managed appropriately.

Doses of AZD2281 in excess of that specified in the Clinical Study Protocol should only be recorded in the CRF as an AE of "overdose" if there are associated clinical symptoms or signs.

An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the CRF.

An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the CRF. In addition, the overdose should be reported on a separate "Clinical Study Overdose Report Form".

An overdose without associated symptoms should not be recorded as an AE in the CRF. The overdose should be reported on a "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

9.4.1 Maternal exposure

The outcomes of any conception occurring from the date of the first dose of study medication (AZD2281 or Caelyx) until 6 months after the last dose must be followed up and documented.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform appropriate AstraZeneca representatives immediately but no later than the end of the next business day of when he or she becomes aware of it. The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the appropriate AstraZeneca Patient Safety data entry site within 30 calendar days.

9.4.2 Paternal exposure

Male patients must refrain from fathering a child during the study and 6 months following the last dose, since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated.

The outcomes of any conception occurring with the patient's partner from the date of the first dose of study medication until 6 months after the last dose must be followed up and documented.

Pregnancy of the subjects partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented.

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Appendix A
Signatures

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse.

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol: Appendix C	
Drug Substance	AZD2281
Study Code	D0810L00001
Appendix Edition Number	Final Version 2.1
Appendix Date	[redacted]

1. COLLECTION AND HANDLING OF PHARMACOKINETIC BLOOD SAMPLES

For the assessment of PK plasma profile of AZD2281 and Caelyx , blood samples will be collected at the following time (see also Figure 1, page 8):

Table 1 Pharmacokinetics study plan

	AZD2281				Caelyx				
	DAY 1	**DAY 2**	**DAY 8**	**DAY 28**	**DAY 1**	**DAY 2**	**DAY 3**	**DAY 8 DAY 15**	**DAY 28**
Cohorts pilot, 1, 3, 5									
- Dose escalation	0, 1, 6, 10*	0, 1, 6, 10*	x**	none	none	0, 1, 2, 6*	x**	x**	x**
- Expansion	0, 0.5, 1, 2, 4, 6, 10*	0, 0.5, 1, 2, 4, 6, 10*	x**	none	none	0, 1, 2, 6*	x**	x**	x**
Cohorts 2, 4, 6									
- Dose escalation	0, 1, 6, 10*	none	x**	x**	0, 1, 2, 6*	x**	none	x**	x**
- Expansion	0, 0.5, 1, 2, 4, 6, 10*	none	x**	x**	0, 1, 2, 6*	x**	none	x**	x**

* hours post dosing
** collection of 1 blood sample

1.1 AZD2281

1.1.1 AZD2281PK Sample Preparation

Venous blood samples (4 mL) will be collected into pre-labelled tubes containing LITHIUM HEPARIN anticoagulant at the times shown in the study plan and thoroughly mixed. Pharmacokinetic sample tubes will be clearly labelled with the compound name, protocol number, subject enrolment code (or centre and patient number), study day, sample number, date of sample collection and nominal time-point. The date and time of sample collection will be recorded on CRFs.

Venous blood samples taken into LITHIUM HEPARIN anticoagulant will be centrifuged at 2000G for 10 minutes at room temperature within 30 minutes of collection, to provide plasma for analysis of AZD2281. Following centrifugation, each plasma sample should be transferred to a separate individually labelled vial and stored at –20ºC within 1 hour of blood collection. Plasma samples should be stored at -20ºC or below at all times until analysis.

1.1.2 Shipment of pharmacokinetic plasma samples for AZD2281 measurement

Plasma samples should be stored at -20°C until the AstraZeneca CRA advises on shipment (approximately once each cohort of 3 patients has been completed). Samples will only be shipped once there are complete profiles for patients.

Plasma samples must be kept at a temperature of –20 ºC or below (using a freezer or dry ice) whilst being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples will remain frozen for at least 72 hours to allow for delays in shipment. Arrival a[redacted]at the weekend and public holidays must be avoided.

The primary contact at[redacted]and the AstraZeneca Monitoring Scientis[redacted] must be notified, by e-mail, of the shipment details (including an electronic copy of the sample manifest) before the samples are shipped. The samples should be addressed as follows:

URGENT
[redacted]

1.2 Caelyx

1.2.1 Caelyx PK Sample Preparation

Venous blood samples (4 mL) will be collected into pre-labelled tubes containing K_3EDTA anticoagulant at the times shown in the study plan (Table 1 and Figure 1). Tubes will be thoroughly mixed, placed on chipped ice and protected from light. Pharmacokinetic sample tubes will be clearly labelled with the compound name, protocol number, subject enrolment code (or centre and patient number), study day, sample number, date of sample collection and nominal time-point. The date and time of sample collection will be recorded on CRFs.

Venous blood samples taken into K_3EDTA anticoagulant will be centrifuged at 1400 g for 10 minutes at 4°C within 30 minutes of collection, to provide plasma for analysis of Caelyx. Following centrifugation, each plasma sample should be transferred to two separated individually labelled polypropylene cryovial and stored at –80ºC within 1 hour of blood collection. Plasma samples should be stored at -80ºC at all times until analysis.

1.2.2 Shipment of pharmacokinetic plasma samples for Caelyx measurement

Plasma samples should be stored at -80°C until the AstraZeneca CRA advises on shipment (approximately once each cohort of 3 patients has been completed). Samples will only be shipped once there are complete profiles for patients.

Plasma samples must be kept at a temperature of –20 ºC or below (using a freezer or dry ice) whilst being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples will remain frozen for at least 72 hours to allow for delays in shipment. Arrival at [redacted] at the weekend and public holidays must be avoided.

The primary contact at [redacted] must be notified, by e-mail, of the shipment details (including an electronic copy of the sample manifest) before the samples are shipped. The samples should be addressed as follows:

URGENT
[redacted]

2. COLLECTION AND HANDLING OF PHARMACODYNAMIC SAMPLES

2.1 Preparation of pharmacodynamic samples

Venous blood samples (8 mL), for determination of histone H2AX phosphorylation in PBMCs, will be taken at the times shown in the study plan (Cycle 1: Day 1, 8, 15, 28. see Fig. 1). Samples will be collected into VACUTAINER CPT Tubes (Becton Dickinson, Franklin Lakes, NJ). Date and time of sample collection will be recorded on the appropriate CRFs After PBMCs isolation, Histone H2AX phosphorylation will be analysed by Flow Cytometry method for intracellular staining using an anti-phospho-H2AX (Ser139) antibody (Cell Signaling Technology, Beverly, MA, USA).

Follow instructions from B to D.

A) SOLUTION and REAGENTS

CPT Tube BD Vacutainer ref 362761 (Becton Dickinson, Franklin Lakes, NJ, USA)
Polypropylene Tube (15 ml)
Phosphate Buffered Saline (1X) (PBS) w/o Ca++ Mg++.
Formaldehyde (methanol free)
Incubation Buffer: Dissolve 0.5 g bovine serum albumin (BSA) in 100mL 1X PBS. Store at 4°C
90% Methanol Solution
EPPENDORF - Safe LockTube 2ml (Eppendorf ref. 0030-120-094)

B) PBMCs PREPARATION

1. Collect the blood sample (8ml) into the Cell Preparation Tube (CPT Becton Dickinson)
2. Invert the drawing tube gently, for several times, to ensure mixing with the anticoagulant. Do not shake. Store the tubes upright at room temperature until centrifugation. (Blood samples should be centrifuged within 30 minutes of collection.)
3. Re-mix the blood samples immediately prior to centrifugation, by gently inverting the tubes .
4. Centrifuge blood samples in a swinging bucket rotor for 30 minutes at 3300 RPM (1800 x g) at 18-25°C.
5. After centrifugation, the peripheral blood mononuclear cells (PBMC) will be found in a diffuse layer just above the gel and in some cases, directly on top of the gel. The upper layer is constituted by plasma. To harvest the PBMCs, invert the unopened CPT tube gently, 5-10 times.
6. Transfer the entire layer above the gel (approximately 7 mL) into the 15 mL polypropylene tube.
7. Add enough phosphate buffered saline 1X (w/o Ca++ and Mg++) to fill the tube. Mix the PBS and the cells by gently inverting and centrifuge in a swinging bucket rotor for 15 min. at 500 x g (1500 RPM) at +4°C. Remove as much supernatant as possible.
8. Resuspend cell pellet in 10 ml of PBS, keep 50 µl of cells for counting by trypan blue staining

NOTE: to avoid creating confusion, the technique for counting the cells should be the one that is routinely used in the respective patient's recruitment centers. Only viable cells should be counted.

9. Aliquot at least 1.5 - 2 x10^6 cells, into each polypropylene tube. Provide two aliquots minimum. If you are left with a 1 ml volume fraction do not discard it, but simply write the number of cells on it.

NOTE : in most cases you will have more than two tubes total.

C) FIXATION

1. Pellet cells by centrifugation for 10 min. at 500 x g (1500 RPM) at +4°C and aspirate supernatant.

2. Resuspend cells briefly in 1 ml PBS (1X). Add formaldehyde to a final concentration of 2-4%formaldehyde.

3. Fix for 10 minutes at 37°C.

4. Chill tubes on ice for 1 minute.

5. Transfer each sample in EPPENDORF Safe LockTube 2ml

D) PERMEABILIZATION

1. To remove fix prior to permeabilization, pellet cells by centrifugation for 15 min. at 1500 RPM at +4°C and resuspend in 1ml of ice-cold 90% methanol, gently vortexing,

2. Incubate tubes 30 minutes on ice.

3. Store cells (PBMCs) at –20°C in 90% methanol.

NOTE: WRAP ACCURATELY EACH TUBE WITH PARAFILM.

- Sample tubes will be clearly labelled with the compound name, protocol number, subject enrolment code (or centre and patient number), study day, sample number, date of sample collection and nominal time-point. The date and time of sample collection will be recorded on appropriate CRFs.

- Once all the samples from one patient who has completed the cycle or had to be dropped out have been collected, contact the ASTRA ZENECA to organize the transport of frozen cells to Milano on dry-ice.Alternatively the shipment will be scheduled as soon as possible.

2.2 Shipment of pharmacodynamic samples

PBMC samples should be stored at -20°C until the AstraZeneca CRA advises on shipment (approximately once cycle 1 of each patient has been completed). Samples will only be shipped once there are complete profiles for patients.

Cell samples must be kept at a temperature of –20 ºC (using a freezer or dry-ice) while being shipped and should be packed securely to avoid breakage during transit. Samples should be double-bagged to contain leaks and packed with a sufficient quantity of dry ice to ensure that the samples will remain frozen for at least 72 hours to allow for delays in shipment. Arrival at

[redacted] at the weekend and public holidays must be avoided.

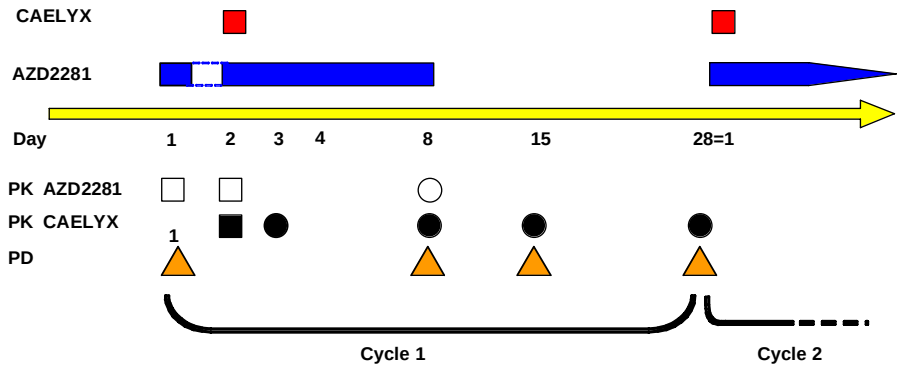
The primary contact at [redacted] must be notified, by e-mail, of the shipment details (including an electronic copy of the sample manifest) before the samples are shipped. The samples should be addressed as follows:

URGENT
D0810L00001 samples

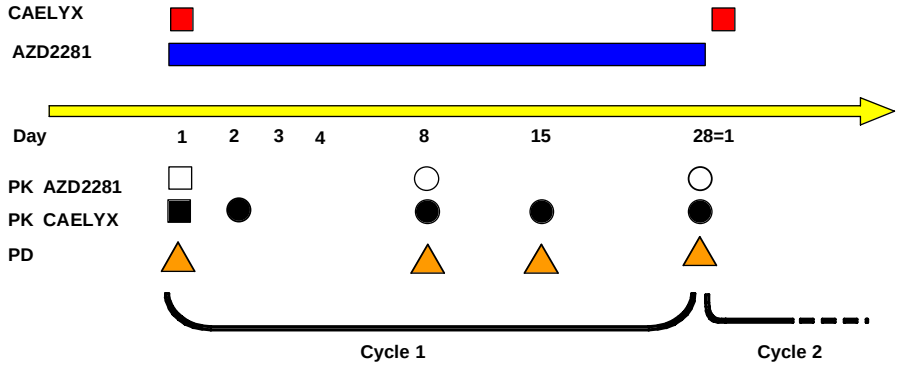
[redacted]

Figure 1 Schedules for Pharmacokinetic Evaluation

SCHEDULE 1: AZD2281 bid for 7 days out of 28-day schedule
CAELYX 40mg/m^2 1h-infusion every 4 weeks



SCHEDULE 2: AZD2281 bid continuously for 4 weeks
CAELYX 40mg/m^2 1h-infusion every 4 weeks



PK AZD2281 — 1 PK SAMPLE FOR AZD2281: Through level

PK DOXIL — 1 PK SAMPLE FOR DOXIL

PD: H2AX phosphorylation in PBMCs

PK AZD2281
Limited during the Dose Escalation Phase : 0, 1, 6, 10 hours post dosing
Full during the Expansion Phase at RD: 0, 0.5, 1, 2, 4, 6, 10 hours post dosing

PK DOXIL
0, 1 (end of infusion), 2, 6, 24, 168 (day8), 336 (day 15), 648 (day 28) hours

Appendix D
Example of Performance Status (ECOG/Karnofsky Scale)

EXAMPLE OF PERFORMANCE STATUS (ECOG/KARNOFSKY SCALE)

Description	ECOG Grade	Karnofsky Equivalent	
Fully active, able to carry on all pre-disease performance without restriction	0	100	Normal, no complaints; no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature ie, light housework, office work	1	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do work.
Ambulatory and capable of self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	60	Requires occasional assistance but is able to care for most of personal needs.
		50	Requires considerable assistance and frequent medical care.
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	40	Disabled; requires special care and assistance.
		30	Severely disabled; hospitalisation is indicated although death not imminent.
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4	20	Very ill; hospitalisation and active supportive care necessary.
		10	Moribund.

AstraZeneca

Clinical Study Protocol : Appendix E	
Drug Substance	AZD2281
Study Code	D0810L00001
Appendix Edition Number	Final Version 2.1
Appendix Date	[redacted]

Appendix E
Cytochrome P450 Isoenzymes: Inducers and Inhibitors

CYTOCHROME P450 ISOENZYMES

AZD2281 is an investigational drug, for which no data on in vivo interactions are currently available. Based on in vitro data and clinical exposure data AZD2281 is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of AZD2281 is CYP3A4 and consequently, although the contribution of metabolic clearance to total drug clearance in man is currently unknown, to ensure patient safety the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving AZD2281.

Whilst this is not an exhaustive list, it covers the known potent inhibitors which have most often previously been reported to be associated with clinically significant drug interactions:

- Ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions, the following CYP3A4 inducers are excluded:

- Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone and St John's Wort (wash-out period for phenobarbitone 5 weeks and for any of the others 3 weeks).

If use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Medical Advisor, and a decision to allow the patient to remain on study will be made on a case-by-case basis.

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Clinical Study Protocol : Appendix F	
Drug Substance	AZD2281
Study Code	D0810L00001
Appendix Edition Number	Final Version 2.1
Appendix Date	[redacted]

Appendix F
Caelyx Summary of Product Characteristics (EMEA)

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LIST OF TABLES

1. NAME OF THE MEDICINAL PRODUCT

Caelyx 2 mg/ml concentrate for solution for infusion ¨

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of Caelyx contains 2 mg doxorubicin hydrochloride in a pegylated liposomal formulation.

Caelyx, a liposome formulation, is doxorubicin hydrochloride encapsulated in liposomes with surfacebound methoxypolyethylene glycol (MPEG). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system (MPS), which increases bloodcirculation time.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion

The suspension is sterile, translucent and red.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Caelyx is indicated:

- As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.
- For treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
- In combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant.
- For treatment of AIDS-related Kaposi’s sarcoma (KS) in patients with low CD4 counts
- (<200 CD4 lymphocytes/mm³) and extensive mucocutaneous or visceral disease.

- Caelyx may be used as first-line systemic chemotherapy, or as second line chemotherapy in AIDS-KS patients with disease that has progressed with, or in patients intolerant to, prior combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and standard doxorubicin (or other anthracycline).

4.2 Posology and method of administration

Caelyx should only be administered under the supervision of a qualified oncologist specialised in th administration of cytotoxic agents.

Caelyx exhibits unique pharmacokinetic properties and must not be used interchangeably with other formulations of doxorubicin hydrochloride.

Breast cancer/Ovarian cancer:

Caelyx is administered intravenously at a dose of 50 mg/m² once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment.

Multiple Myeloma:

Caelyx is administered at 30 mg/m² on day 4 of the bortezomib 3 week regimen as a 1 hour infusion administered immediately after the bortezomib infusion. The bortezomib regimen consists of 1.3 mg/m² on days 1, 4, 8, and 11 every 3 weeks. The dose should be repeated as long as patients respond satisfactorily and tolerate treatment. Day 4 dosing of both medicinal products may be delayed up to 48 hours as medically necessary. Doses of bortezomib should be at least 72 hours apart.

For doses <90 mg: dilute Caelyx in 250 ml 5% (50 mg/ml) glucose solution for infusion.

For doses ≥90 mg: dilute Caelyx in 500 ml 5% (50 mg/ml) glucose solution for infusion.

To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent Caelyx infusions may be administered over a 60-minute period.

In those patients who experience an infusion reaction, the method of infusion should be modified as follows:

5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

AIDS-related KS:

Caelyx is administered intravenously at 20 mg/m² every two-to-three weeks. Avoid intervals shorter than 10 days as medicinal product accumulation and increased toxicity cannot be ruled out. Treatment of patients for two-to-three months is recommended to achieve a therapeutic response. Continue treatment as needed to maintain a therapeutic response.

The dose of Caelyx is diluted in 250 ml 5% (50 mg/ml) glucose solution for infusion and administered by intravenous infusion over 30 minutes.

For all patients:

If the patient experiences early symptoms or signs of infusion reaction (see Sections 4.4 and 4.8), immediately discontinue the infusion, give appropriate premedications (antihistamine and/or short acting corticosteroid) and restart at a slower rate.

Do not administer Caelyx as a bolus injection or undiluted solution. It is recommended that the Caelyx infusion line be connected through the side port of an intravenous infusion of 5% (50 mg/ml) glucose to achieve further dilution and minimise the risk of thrombosis and extravasation. The infusion may be given through a peripheral vein. Do not use with in-line filters. Caelyx must not be given by the intramuscular or subcutaneous route (see Section 6.6).

To manage adverse events such as palmar-plantar erythrodysesthesia (PPE), stomatitis or haematological toxicity, the dose may be reduced or delayed. Guidelines for Caelyx dose modification secondary to these adverse effects are provided in the tables below. The toxicity grading in these tables is based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC).

The tables for PPE (Table 10) and stomatitis (Table 11) provide the schedule followed for dose modification in clinical trials in the treatment of breast or ovarian cancer (modification of the recommended 4 week treatment cycle): if these toxicities occur in patients with AIDS related KS, the recommended 2 to 3 week treatment cycle can be modified in a similar manner.

The table for haematological toxicity (Table 12) provides the schedule followed for dose modification in clinical trials in the treatment of patients with breast or ovarian cancer only. Dose modification in patients with AIDS-KS is addressed in 4.8

Guidelines For Caelyx Dose Modification

Table 10 PALMAR – PLANTAR ERYTHRODYSESTHESIA

Toxicity Grade At Current Assessment	Week After Prior Caelyx Dose		
	Week 4	**Week 5**	**Week 6**
Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Redose unless** patient has experienced a previous Grade 3 or 4 skin toxicity, in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval**
Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm in diameter)	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval**
Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**
Grade 4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalization)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**

Table 11 STOMATITIS

	Week after Prior Caelyx Dose		
Toxicity Grade At Current Assessment	**4**	**5**	**6**
Grade 1 (painless ulcers, erythema, or mild soreness)	**Redose unless** patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Redose unless** patient has experienced a previous Grade 3 or 4 stomatitis in which case wait an additional week	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment
Grade 2 (painful erythema, oedema, or ulcers, but can eat)	**Wait an additional week**	**Wait an additional week**	**Decrease dose by 25%; return to 4 week interval** or withdraw patient per physician's assessment
Grade 3 (painful erythema, edema, or ulcers, but cannot eat)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**
Grade 4 (requires parenteral or enteral support)	**Wait an additional week**	**Wait an additional week**	**Withdraw patient**

Table 12 HAEMATOLOGICAL TOXICITY (ANC OR PLATELETS) – MANAGEMENT OF PATIENTS WITH BREAST OR OVARIAN CANCER

GRADE	ANC	PLATELETS	MODIFICATION
Grade 1	1,500 – 1,900	75,000 – 150,000	Resume treatment with no dose reduction.
Grade 2	1,000 – <1,500	50,000 – <75,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
Grade 3	500 – <1,000	25,000 – <50,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
Grade 4	<500	<25,000	Wait until ANC ≥1,500 and platelets ≥75,000; decrease dose by 25% or continue full dose with growth factor support.

For multiple myeloma patients treated with Caelyx in combination with bortezomib who experience PPE or stomatitis, the Caelyx dose should be modified as described in Table 10 and 2 above respectively. Table 13, below provides the schedule followed for other dose modifications in the clinical trial in the treatment of patients with multiple myeloma receiving Caelyx and bortezomib combination therapy. For more detailed information on bortezomib dosing and dosage adjustments, see the SPC for bortezomib.

Table 13 DOSAGE ADJUSTMENTS FOR CAELYX + BORTEZOMIB COMBINATION THERAPY -PATIENTS WITH MULTIPLE MYELOMA

Patient Status	Caelyx	Bortezomib
Fever ≥38°Cand ANC <1,000/mm³	Do not dose this cycle if before Day 4; if after Day 4, reduce next dose by 25%.	Reduce next dose by 25%.
On any day of medicine administration after Day 1 of each cycle: Platelet count <25,000/mm³ Hemoglobin <8 g/dl ANC <500/mm³	Do not dose this cycle if before Day 4; if after Day 4 reduce next dose by 25% in the following cycles if bortezomib is reduced for hematologic toxicity.*	Do not dose; if 2 or more doses are not given in a cycle, reduce dose by 25% in following cycles.
Grade 3 or 4 non-hematologic medicine related toxicity	Do not dose until recovered to Grade <2 and reduce dose by 25% for all subsequent doses.	Do not dose until recovered to Grade <2 and reduce dose by 25% for all subsequent doses.
Neuropathic pain or peripheral neuropathy	No dosage adjustments.	See the SPC for bortezomib.

Patients with impaired hepatic function: Caelyx pharmacokinetics determined in a small number of patients with elevated total bilirubin levels do not differ from patients with normal total bilirubin; however, until further experience is gained, the Caelyx dosage in patients with impaired hepatic function should be reduced based on the experience from the breast and ovarian clinical trial programs as follows: at initiation of therapy, if the bilirubin is between 1.2 - 3.0 mg/dl, the first dose is reduced by 25%. If the bilirubin is >3.0 mg/dl, the first dose is reduced by 50%. If the patient tolerates the first dose without an increase in serum bilirubin or liver enzymes, the dose for cycle 2 can be increased to the next dose level, i.e., if reduced by 25% for the first dose, increase to full dose for cycle 2; if reduced by 50% for the first dose, increase to 75% of full dose for cycle 2. The dosage can be increased to full dose for subsequent cycles if tolerated. Caelyx can be administered to patients with liver metastases with concurrent elevation of bilirubin and liver enzymes up to 4 x the upper limit of the normal range. Prior to Caelyx administration, evaluate hepatic function using conventional clinical laboratory tests such as ALT/AST, alkaline phosphatase, and bilirubin.

Patients with impaired renal function: As doxorubicin is metabolised by the liver and excreted in the bile, dose modification should not be required. Population pharmaco-kinetic data (in the range of creatinine clearance tested of 30 - 156 ml/min) demonstrate that Caelyx clearance is not influenced by renal function. No pharmaco-kinetic data are available in patients with creatinine clearance of less than 30 ml/min.

AIDS-KS patients with splenectomy: As there is no experience with Caelyx in patients who have had splenectomy, treatment with Caelyx is not recommended.

Paediatric patients: The experience in children is limited. Caelyx is not recommended in patients below 18 years of age.

Elderly patients: Population based analysis demonstrates that age across the range tested (21 – 75 years) does not significantly alter the pharmacokinetics of Caelyx.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.

Caelyx must not be used to treat AIDS-KS that may be treated effectively with local therapy or systemic alfa-interferon.

4.4 Special warnings and precautions for use

Cardiac toxicity: It is recommended that all patients receiving Caelyx routinely undergo frequent ECG monitoring. Transient ECG changes such as T-wave flattening, S-T segment depression and benign arrhythmias are not considered mandatory indications for the suspension of Caelyx therapy. However, reduction of the QRS complex is considered more indicative of cardiac toxicity. If this change occurs, the most definitive test for anthracycline myocardial injury, i.e., endomyocardial biopsy, must be considered.

More specific methods for the evaluation and monitoring of cardiac functions as compared to ECG are a measurement of left ventricular ejection fraction by echo-cardiography or preferably by Multigated Angiography (MUGA). These methods must be applied routinely before the initiation of Caelyx therapy and repeated periodically during treatment. The evaluation of left ventricular function is considered to be mandatory before each additional administration of Caelyx that exceeds a lifetime cumulative anthracycline dose of 450 mg/m². The evaluation tests and methods mentioned above concerning the monitoring of cardiac performance during anthracycline therapy are to be employed in the following order: ECG monitoring, measurement of left ventricular ejection fraction, endomyocardial biopsy. If a test result indicates possible cardiac injury associated with Caelyx therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

In patients with cardiac disease requiring treatment, administer Caelyx only when the benefit outweighs the risk to the patient.

Exercise caution in patients with impaired cardiac function who receive Caelyx.

Whenever cardiomyopathy is suspected, i.e., the left ventricular ejection fraction has substantially decreased relative to pre-treatment values and/or left ventricular ejection fraction is lower than a prognostically relevant value (e.g. <45%), endomyocardial biopsy may be considered and the benefit of continued therapy must be carefully evaluated against the risk of developing irreversible cardiac damage.

Congestive heart failure due to cardiomyopathy may occur suddenly, without prior ECG changes and may also be encountered several weeks after discontinuation of therapy.

Caution must be observed in patients who have received other anthracyclines. The total dose of doxorubicin hydrochloride must also take into account any previous (or concomitant) therapy with cardiotoxic compounds such as other anthracyclines/-anthraquinones or e.g. 5-fluorouracil. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450 mg/m² in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.

The cardiac safety profile for the dosing schedule recommended for both breast and ovarian cancer (50 mg/m²) is similar to the 20 mg/m² profile in patients with AIDS-KS (see Section 4.8).

Myelosuppression: Many patients treated with Caelyx have baseline myelosuppression due to such factors as their pre-existing HIV disease or numerous concomitant or previous medications, or tumours involving bone marrow. In the pivotal trial in patients with ovarian cancer treated at a dose of 50 mg/m², myelosuppression was generally mild to moderate, reversible, and was not associated with episodes of neutropaenic infection or sepsis. Moreover, in a controlled clinical trial of Caelyx vs. topotecan, the incidence of treatment related sepsis was substantially less in the Caelyx-treated ovarian cancer patients as compared to the topotecan treatment group. A similar low incidence of myelosuppression was seen in patients with metastatic breast cancer receiving Caelyx in a first-line clinical trial. In contrast to the experience in patients with breast cancer or ovarian cancer, myelosuppression appears to be the dose-limiting adverse event in patients with AIDS-KS (see Section 4.8). Because of the potential for bone marrow suppression, periodic blood counts must be performed frequently during the course of Caelyx therapy, and at a minimum, prior to each dose of Caelyx.

Persistent severe myelosuppression, may result in superinfection or haemorrhage.

In controlled clinical studies in patients with AIDS-KS against a bleomycin/vincristine regimen, opportunistic infections were apparently more frequent during treatment with Caelyx. Patients and doctors must be aware of this higher incidence and take action as appropriate.

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin.

Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Given the difference in pharmacokinetic profiles and dosing schedules, Caelyx should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Infusion-associated reactions: Serious and sometimes life-threatening infusion reactions, which are characterised by allergic-like or anaphylactoid-like reactions, with symptoms including asthma, flushing, urticarial rash, chest pain, fever, hypertension, tachycardia, pruritus, sweating, shortness of breath, facial oedema, chills, back pain, tightness in the chest and throat and/or hypotension may occur within minutes of starting the infusion of Caelyx. Very rarely, convulsions also have been observed in relation to infusion reactions (see Section 4.8). Temporarily stopping the infusion usually resolves these symptoms without further therapy. However, medications to treat these symptoms (e.g., antihistamines, corticosteroids, adrenaline, and anticonvulsants), as well as emergency equipment should be available for immediate use. In most patients treatment can be resumed after all symptoms have resolved, without recurrence. Infusion reactions rarely recur after the first treatment cycle. To minimise the risk of infusion reactions, the initial dose should be administered at a rate no greater than 1 mg/minute (see Section 4.2).

Diabetic patients: Please note that each vial of Caelyx contains sucrose and the dose is administered in 5% (50 mg/ml) glucose solution for infusion.

For common adverse events which required dose modification or discontinuation see Section 4.8.

4.5 Interaction with other medicinal products and other forms of interaction

No formal medicinal product interaction studies have been performed with Caelyx, although phase II combination trials with conventional chemotherapy agents have been conducted in patients with gynaecological malignancies. Exercise caution in the concomitant use of medicinal products known to interact with standard doxorubicin hydrochloride. Caelyx, like other doxorubicin hydrochloride preparations, may potentiate the toxicity of other anti-cancer therapies. During clinical trials in patients with solid tumours (including breast and ovarian cancer) who have received concomitant cyclophosphamide or taxanes, no new additive toxicities were noted. In patients with AIDS**,** exacerbation of cyclophosphamide-induced haemorrhagic cystitis and enhancement of the hepatotoxicity of 6-mercaptopurine have been reported with standard doxorubicin hydrochloride.

Caution must be exercised when giving any other cytotoxic agents, especially myelotoxic agents, at the same time.

4.6 Pregnancy and lactation

Pregnancy: Doxorubicin hydrochloride is suspected to cause serious birth defects when administered during pregnancy. Therefore, Caelyx should not be used during pregnancy

unless clearly necessary. Women of child-bearing potential must be advised to avoid pregnancy while they or their male partner are receiving Caelyx and in the six months following discontinuation of Caelyx therapy (see Section 5.3).

Lactation: It is not known whether Caelyx is excreted in human milk. Because many medicinal products, including anthracyclines, are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, therefore mothers must discontinue nursing prior to beginning Caelyx treatment. Health experts recommend that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

4.7 Effects on ability to drive and use machines

Caelyx has no or negligible influence on the ability to drive and use machines. However, in clinical studies to date, dizziness and somnolence were associated infrequently (<5%) with the administration of Caelyx. Patients who suffer from these effects must avoid driving and operating machinery.

4.8 Undesirable effects

The most common undesirable effect reported in breast/ovarian clinical trials (50 mg/m² every 4 weeks) was palmar-plantar erythrodysesthesia (PPE). The overall incidence of PPE reported was 44.0% - 46.1%. These effects were mostly mild, with severe (Grade III) cases reported in 17% - 19.5%. The reported incidence of life-threatening (Grade IV) cases was <1%. PPE infrequently resulted in permanent treatment discontinuation (3.7% - 7.0%). PPE is characterised by painful, macular reddening skin eruptions. In patients experiencing this event, it is generally seen after two or three cycles of treatment. Improvement usually occurs in one - two weeks, and in some cases, may take up to 4 weeks or longer for complete resolution. Pyridoxine at a dose of 50 - 150 mg per day and corticosteroids have been used for the prophylaxis and treatment of PPE, however, these therapies have not been evaluated in phase III trials. Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with Caelyx include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting). PPE appears to be primarily related to the dose schedule and can be reduced by extending the dose interval 1 - 2 weeks (see Section 4.2).

However, this reaction can be severe and debilitating in some patients and may require discontinuation of treatment. Stomatitis/mucositis and nausea were also commonly reported in breast/ovarian cancer patient populations, whereas the AIDS-KS Program (20 mg/m² every 2 weeks), myelosuppression (mostly leukopaenia) was the most common side effect (see AIDS-KS). PPE was reported in 16% of multiple myeloma patients treated with Caelyx plus bortezomib combination therapy. Grade 3 PPE was reported in 5% of patients. No grade 4 PPE was reported. The most frequently reported (medicine-related treatment-emergent) adverse events in combination therapy (Caelyx + bortezomib) were nausea (40%), diarrhoea

(35%), neutropaenia (33%), thrombocytopaenia (29%), vomiting (28%), fatigue (27%), and constipation (22%).

Breast cancer program: 509 patients with advanced breast cancer who had not received prior chemotherapy for metastatic disease were treated with Caelyx (n=254) at a dose of 50 mg/m² every 4 weeks, or doxorubicin (n=255) at a dose of 60 mg/m² every 3 weeks, in a phase III clinical trial (I97- 328). The following common adverse events were reported more often with doxorubicin than with Caelyx: nausea (53% vs. 37%; Grade III/IV 5% vs. 3%), vomiting (31% vs. 19%; Grade III/IV 4% vs. less than 1%), any alopecia (66% vs. 20%), pronounced alopecia (54% vs.7%), and neutropaenia (10% vs. 4%; Grade III/IV 8% vs. 2%). Mucositis (23% vs. 13%; Grade III/IV 4% vs. 2%), and stomatitis (22% vs. 15%; Grade III/IV 5% vs. 2%) were reported more commonly with Caelyx than with doxorubicin. The average duration of the most common severe (Grade III/IV) events for both groups was 30 days or less. See Table 14 for complete listing of undesirable effects reported in Caelyx-treated patients. The incidence of life threatening (Grade IV) haematologic effects was <1.0% and sepsis was reported in 1% of patients. Growth factor support or transfusion support was necessary in 5.1% and 5.5% of patients, respectively (see Section 4.2).

Clinically significant laboratory abnormalities (Grades III and IV) in this group was low with elevated total bilirubin, AST and ALT reported in 2.4%, 1.6% and <1% of patients respectively. No clinically significant increases in serum creatinine were reported.

Table 14 Treatment Related Undesirable Effects Reported in Breast Cancer Clinical Trials (50 mg/m² every 4 weeks) (Caelyx-treated patients) by Severity, MedDRA System Organ Class and Preferred Term

Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100)

CIOMS III

AE by body system	Breast Cancer All Severities n=254 (≥5%)	Breast Cancer Grades III/IV n=254 (≥5%)	Breast Cancer n=404 (1-5%) not previously reported in clinical trials
Infections and infestations			
Common	Pharyngitis		Folliculitis, fungal infection, cold sores (non-herpetic), upper respiratory tract infection
Uncommon		Pharyngitis	

AE by body system	Breast Cancer All Severities n=254 (≥5%)	Breast Cancer Grades III/IV n=254 (≥5%)	Breast Cancer n=404 (1-5%) not previously reported in clinical trials
Blood and lymphatic system disorders			
Common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Leukopaenia, anaemia	Thrombocythemia
Uncommon		Neutropaenia	
Metabolism and nutrition disorders			
Very Common	Anorexia		
Common		Anorexia	
Nervous system disorders			
Common	Paresthesia	Paresthesia	Peripheral neuropathy
Uncommon	Somnolence		
Eye Disorders Common			Lacrimation, blurred vision
Cardiac disorders Common			Ventricular arrhythmia
Respiratory, thoracic and mediastinal disorders Common			Epistaxis
Gastrointestinal disorders			
Very Common	Nausea, stomatitis, vomiting		
Common	Abdominal pain, constipation, diarrhoea, dyspepsia, mouth ulceration	Abdominal pain, diarrhoea, nausea, stomatitis	Oral pain
Uncommon		Mouth ulceration, constipation, Vomiting	

AE by body system	Breast Cancer All Severities n=254 (≥5%)	Breast Cancer Grades III/IV n=254 (≥5%)	Breast Cancer n=404 (1-5%) not previously reported in clinical trials
Skin and subcutaneous tissue disorders			
Very Common	PPE*, alopecia, rash	PPE*	
Common	Dry skin, skin discolouration, pigmentation abnormal, erythema	Rash	Bullous eruption, dermatitis, erythematous rash, nail disorder, scaly skin
Uncommon		Pigmentation abnormal, erythema	
Musculoskeletal and connective tissue disorders			
Common			Leg cramps, bone pain, musculoskeletal pain
Reproductive system and breast disorders			
Common			Breast pain
General disorders and administration site conditions			
Very Common	Asthenia, fatigue, mucositis NOS		
Common	Weakness, fever, pain	Asthenia, mucositis NOS	Oedema, leg oedema.
Uncommon		Fatigue, weakness, pain	

*Ovarian cancer program***:** 512 patients with ovarian cancer (a subset of 876 solid tumour patients) were treated with Caelyx at a dose of 50 mg/m² in clinical trials. See Table 15 for undesirable effects reported in Caelyx-treated patients.

Table 15 Treatment Related Undesirable Effects Reported in Ovarian Cancer Clinical Trials (50 mg/m² every 4 weeks) (Caelyx-treated patients)by Severity, MedDRA System Organ Class and Preferred Term

Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100)

CIOMS III

AE by body system	Ovarian Cancer All Severities n=512 (≥5 %)	Ovarian Cancer Grades III/IV n=512 (≥5 %)	Ovarian Cancer n=512 (1-5%)
Infections and infestations			
Common	Pharyngitis		Infection, oral moniliasis, herpes zoster, urinary tract infection
Uncommon		Pharyngitis	
Blood and lymphatic system disorders			
Very Common	Leukopaenia, anaemia, neutropaenia, thrombocytopaenia	Neutropaenia	
Common		Leukopaenia, anaemia, thrombocytopaenia	Hypochromic anaemia
Immune system disorders			
Common			Allergic reaction
Metabolism and nutrition disorders			
Very Common	Anorexia		
Common			Dehydration, cachexia
Uncommon		Anorexia	
Psychiatric disorders			
Common			Anxiety, depression, insomnia

AE by body system	Ovarian Cancer All Severities n=512 (≥5 %)	Ovarian Cancer Grades III/IV n=512 (≥5 %)	Ovarian Cancer n=512 (1-5%)
Nervous system disorders			
Common	Paresthesia, somnolence		Headache, dizziness, neuropathy, hypertonia
Uncommon		Paresthesia, somnolence	
Eye disorders			
Common			Conjunctivitis
Cardiac disorders			
Common			Cardiovascular disorder
Vascular disorders			
Common			Vasodilatation
Respiratory, thoracic and mediastinal disorders			
Common			Dyspnoea, increased cough
Gastrointestinal disorders			
Very Common	Constipation, diarrhoea, nausea, stomatitis, vomiting		
Common	Abdominal pain, dyspepsia, mouth ulceration	Nausea, stomatitis, vomiting, abdominal pain, diarrhoea	Mouth ulceration, esophagitis, nausea and vomiting, gastritis, dysphagia, dry mouth, flatulence, gingivitis, taste perversion
Uncommon		Constipation, dyspepsia, mouth ulceration	

AE by body system	Ovarian Cancer All Severities n=512 (≥5 %)	Ovarian Cancer Grades III/IV n=512 (≥5 %)	Ovarian Cancer n=512 (1-5%)
Skin and subcutaneous tissue disorders			
Very Common	PPE*, alopecia, rash	PPE*	
Common	Dry skin, skin discolouration	Alopecia, rash	Vesiculobullous rash, pruritus, exfoliative dermatitis, skin disorder, maculopapular rash, sweating, acne, skin ulcer
Musculoskeletal and connective tissue disorders			
Common			Back pain, myalgia
Renal and urinary disorders			
Common			Dysuria
Reproductive system and breast disorders			
Common			Vaginitis
General disorders and administration site conditions			
Very Common	Asthenia, mucous membrane disorder		
Common	Fever, pain	Asthenia, mucous membrane disorder, pain	Chills, chest pain, malaise, peripheral oedema
Uncommon		Fever	
Investigation			
Common			Weight loss

* palmar-plantar erythrodysesthesia (Hand- foot syndrome).

Myelosuppression was mostly mild or moderate and manageable. Sepsis related to leukopaenia was observed infrequently (<1%). Growth factor support was required infrequently (<5%) and transfusion support was required in approximately 15% of patients (see Section 4.2).

In a subset of 410 patients with ovarian cancer, clinically significant laboratory abnormalities occurring in clinical trials with Caelyx included increases in total bilirubin (usually in patients with liver metastases) (5%) and serum creatinine levels (5%). Increases in AST were less frequently (<1%) reported.

Solid tumour patients: in a larger cohort of 929 patients with solid tumours (including breast cancer and ovarian cancer) predominantly treated at a dose of 50 mg/m² every 4 weeks, the safety profile and incidence of adverse effects are comparable to those of the patients treated in the pivotal breast cancer and ovarian cancer trials.

Multiple Myeloma program:

Of 646 patients with multiple myeloma who have received at least 1 prior therapy, 318 patients were treated with combination therapy of Caelyx 30 mg/m² as a one hour intra-venous infusion administered on day 4 following bortezomib which is administered at 1.3 mg/m² on days 1, 4, 8, and 11, every three weeks or with bortezomib monotherapy in a phase III clinical trial.

See Table 16 for adverse effects reported in 5% patients treated with combination therapy of Caelyx plus bortezomib.

Neutropaenia, thrombocytopaenia, and anaemia were the most frequently reported hematologic events reported with both combination therapy of Caelyx plus bortezomib and bortezomib monotherapy. The incidence of grade 3 and 4 neutropaenia was higher in the combination therapy group than in the monotherapy group (28% vs. 14%). The incidence of grade 3 and 4 thrombocytopaenia was higher in the combination therapy group than in the monotherapy group (22% vs. 14%). The incidence of anaemia was similar in both treatment groups (7% vs. 5%).

Stomatitis was reported more frequently in the combination therapy group (16%) than in the monotherapy group (3%), and most cases were grade 2 or less in severity. Grade 3 stomatitis was reported in 2% of patients in the combination therapy group. No grade 4 stomatitis was reported. Nausea and vomiting were reported more frequently in the combination therapy group (40% and 28%) than in the monotherapy group (32% and 15%) and were mostly grade 1 and 2 in severity.

Treatment discontinuation of one or both agents due to adverse events was seen in 38% of patients.

Common adverse events which led to treatment discontinuation of bortezomib and Caelyx included PPE, neuralgia, peripheral neuropathy, peripheral sensory neuropathy, thrombocytopaenia, decreased ejection fraction, and fatigue.

Table 16 Treatment Related Undesirable Effects Reported in Multiple Myeloma Clinical Trial (Caelyx 30 mg/m² in combination with bortezomib every 3 weeks) by Severity, MedDRA System Organ Class and Preferred Term

Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100)

CIOMS III

AE by body system	All Severities n=318 (≥5 %)	Grades III/IV** n=318 (≥5 %)	All Severities n=318 (1-5 %)
Infections and infestations			
Common	Herpes simplex, herpes zoster	Herpes zoster	Pneumonia, nasopharyngitis, upper respiratory tract infection, oral candidiasis
Blood and lymphatic system disorders			
Very Common	Anaemia, neutropaenia, thrombocytopaenia	Neutropaenia, thrombocytopaenia	
Common	Leukopaenia	Anaemia, leukopaenia	Febrile neutropaenia, lymphopaenia
Metabolism and Nutrition disorders			
Very Common	Anorexia	Anorexia	Dehydration, hypokalaemia, hyperkalaemia,
Common	Decreased appetite		hypomagnesaemia, hyponatraemia, hypocalcaemia
Uncommon		Decreased appetite	
Psychiatric disorders			
Common	Insomnia		Anxiety

AE by body system	All Severities n=318 (≥5 %)	Grades III/IV** n=318 (≥5 %)	All Severities n=318 (1-5 %)
Nervous system disorders			
Very Common	Peripheral sensory neuropathy, neuralgia, headache		
Common	Neuropathy peripheral, neuropathy, paraesthesia, polyneuropathy, dizziness, dysgeusia	Neuralgia, peripheral neuropathy, neuropathy	Lethargy, hypoaesthesia, syncope, dysaesthesia
Uncommon		Headache, peripheral sensory neuropathy, paraesthesia, dizziness	
Eye disorders			
Common			Conjunctivitis
Vascular disorders			
Common			Hypotension, orthostatic hypotension, flushing, hypertension, phlebitis
Respiratory, thoracic, and mediastinal disorders			
Common	Dyspnoea		Cough, epistaxis exertional dyspnoea
Uncommon		Dyspnoea	

AE by body system	All Severities n=318 (≥5 %)	Grades III/IV** n=318 (≥5 %)	All Severities n=318 (1-5 %)
Gastrointestinal disorders			
Very Common	Nausea, diarrhoea, vomiting, constipation, stomatitis		
Common	Abdominal pain, dyspepsia	Nausea, diarrhoea, vomiting, stomatitis	Upper abdominal pain, mouth ulceration, dry mouth, dysphagia, aphthous stomatitis
Uncommon		Constipation, abdominal pain, dyspepsia	
Skin and subcutaneous tissue disorders			
Very Common	PPE*, rash		Pruritus, papular rash, allergic dermatitis, erythema, skin
Common	Dry skin		hyperpigmentation, petechiae, alopecia, medicine eruption
Uncommon		PPE* Rash	
Musculoskeletal and connective tissue disorders			
Common	Pain in extremity		Arthralgia, myalgia, muscle spasms, muscular weakness, musculoskeletal pain, musculoskeletal chest pain
Reproductive system and breast disorders			
Common			Scrotal erythema

AE by body system	All Severities n=318 (≥5 %)	Grades III/IV** n=318 (≥5 %)	All Severities n=318 (1-5 %)
General disorders and administration site conditions			
Very Common	Asthenia, fatigue, pyrexia		
Common		Asthenia, fatigue	Peripheral oedema, chills, influenza-like illness, malaise, hyperthermia
Uncommon		Pyrexia	
Investigations			
Common	Weight decreased		Aspartate aminotransferase increased, ejection fraction decreased, blood creatinine increased, alanine aminotransferase increased

* Palmar-plantar erythrodysesthesia (Hand-foot syndrome).
** Grade 3/4 adverse events are based on the adverse event terms of all severities with an overall incidence ≥5% (see adverse events listed in first column).

AIDS-KS program :

Clinical studies on AIDS-KS patients treated at 20 mg/m² with Caelyx show that myelosuppression was the most frequent undesirable effect considered related to Caelyx occurring very commonly (in approximately one-half of the patients).

Leukopaenia is the most frequent undesirable effect experienced with Caelyx in this population; neutropaenia, anaemia and thrombocytopaenia have been observed. These effects may occur early on in treatment. Haematological toxicity may require dose reduction or suspension or delay of therapy.

Temporarily suspend Caelyx treatment in patients when the ANC count is <1,000/mm³ and/or the platelet count is <50,000/mm³. G-CSF (or GM-CSF) may be given as concomitant therapy to support the blood count when the ANC count is <1,000/mm³ in subsequent cycles. The haematological toxicity for ovarian cancer patients is less severe than in the AIDS-KS setting (see section for ovarian cancer patients above).

Respiratory undesirable effects commonly occurred in clinical studies of Caelyx and may be related to opportunistic infections in the AIDS population. Opportunistic infections (OI's) are observed in KS patients after administration with Caelyx, and are frequently observed in

patients with HIV-induced immunodeficiency. The most frequently observed OI's in clinical studies were candidiasis, cytomegalovirus, herpes simplex, Pneumocystis carinii pneumonia, and mycobacterium avium complex.

Undesirable effects observed in patients with AIDS-KS according to CIOMS III frequency categories (Very common (>1/10); Common (>1/100, <1/10); Uncommon (>1/1,000, <1/100)) were as follows:

Infections and infestations:
Common: oral moniliasis

Blood and lymphatic system disorders:
Very common: neutropaenia, anaemia, leukopaenia
Common: thrombocytopaenia

Metabolism and nutrition disorders:
Common: anorexia

Psychiatric disorders:
Uncommon: confusion

Nervous system disorders:
Common**:** dizziness
Uncommon: paresthesia

Eye disorders:
Common: retinitis

Vascular disorders:
Common: vasodilatation

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea

Gastrointestinal disorders:
Very common: nausea
Common**:** diarrhoea, stomatitis, vomiting, mouth ulceration, abdominal pain, glossitis, constipation, nausea and vomiting

Skin and subcutaneous tissue disorders:
Common: alopecia, rash
Uncommon: palmar-plantar erythrodysesthesia (PPE)

General disorders and administration site conditions:
Common: asthenia, fever, infusion-associated acute reactions

Investigations:
Common: weight loss.

Other less frequently (<5%) observed undesirable effects included hypersensitivity reactions including anaphylactic reactions. Following marketing, bullous eruption has been reported rarely in this population.

Clinically significant laboratory abnormalities frequently (5%) occurred including increases in alkaline phosphatase; AST and bilirubin which were believed to be related to the underlying disease and not Caelyx. Reduction in haemoglobin and platelets were less frequently (<5%) reported. Sepsis related to leukopaenia was rarely (<1%) observed. Some of these abnormalities may have been related to the underlying HIV infection and not Caelyx.

*All patients***:** 100 out of 929 patients (10.8%) with solid tumours were described as having an infusion-associated reaction during treatment with Caelyx as defined by the following Costart terms: allergic reaction, anaphylactoid reaction, asthma, face oedema, hypotension, vasodilatation, urticaria, back pain, chest pain, chills, fever, hypertension, tachycardia, dyspepsia, nausea, dizziness, dyspnoea, pharyngitis, rash, pruritus, sweating, injection site reaction and medicinal product interaction.

Permanent treatment discontinuation was infrequently reported at 2%. A similar incidence of infusion reactions (12.4%) and treatment discontinuation (1.5%) was observed in the breast cancer program**.**

In patients with multiple myeloma receiving Caelyx plus bortezomib, infusion-associated reactions have been reported at a rate of 3%. In patients with AIDS-KS, infusion-associated reactions, were characterised by flushing, shortness of breath, facial oedema, headache, chills, back pain, tightness in the chest and throat and/or hypotension and can be expected at the rate of 5% to 10%. Very rarely, convulsions have been observed in relation to infusion reactions. In all patients, infusion associated

reactions occurred primarily during the first infusion. Temporarily stopping the infusion usually resolves these symptoms without further therapy. In nearly all patients, Caelyx treatment can be resumed after all symptoms have resolved without recurrence. Infusion reactions rarely recur after the first treatment cycle with Caelyx (see Section 4.2).

Myelosuppression associated with anaemia, thrombocytopaenia, leukopaenia, and rarely febrile neutropaenia, has been reported in Caelyx -treated patients.

Stomatitis has been reported in patients receiving continuous infusions of conventional doxorubicin hydrochloride and was frequently reported in patients receiving Caelyx. It did not interfere with patients completing therapy and no dosage adjustments are generally required, unless stomatitis is affecting a patient’s ability to eat. In this case, the dose interval may be extended by 1 - 2 weeks or the dose reduced (see Section 4.2).

An increased incidence of congestive heart failure is associated with doxorubicin therapy at cumulative lifetime doses >450 mg/m² or at lower doses for patients with cardiac risk factors.

Endomyocardial biopsies on nine of ten AIDS-KS patients receiving cumulative doses of Caelyx greater than 460 mg/m² indicate no evidence of anthracycline-induced cardio-myopathy. The recommended dose of Caelyx for AIDS-KS patients is 20 mg/m² every two-to-three weeks. The cumulative dose at which cardiotoxicity would become a concern for these AIDS-KS patients (>400 mg/m²) would require more than 20 courses of Caelyx therapy over 40 to 60 weeks.

In addition, endomyocardial biopsies were performed in 8 solid tumour patients with cumulative anthracycline doses of 509 mg/m² – 1,680 mg/m² . The range of Billingham cardiotoxicity scores was grades 0 - 1.5. These grading scores are consistent with no or mild cardiac toxicity.

In the pivotal phase III trial versus doxorubicin, 58/509 (11.4%) randomized subjects (10 treated with Caelyx at a dose of 50 mg/m²/every 4 weeks versus 48 treated with doxorubicin at a dose of 60 mg/m²/every 3 weeks) met the protocol-defined criteria for cardiac toxicity during treatment and/or follow-up. Cardiac toxicity was defined as a decrease of 20 points or greater from baseline if the resting LVEF remained in the normal range or a decrease of 10 points or greater if the LVEF became abnormal (less than the lower limit for normal). None of the 10 Caelyx subjects who had cardiac toxicity by LVEF criteria developed signs and symptoms of CHF. In contrast, 10 of 48 doxorubicin subjects who had cardiac toxicity by LVEF criteria also developed signs and symptoms of CHF.

In patients with solid tumours, including a subset of patients with breast and ovarian cancers, treated at a dose of 50 mg/m²/cycle with lifetime cumulative anthracycline doses up to 1,532 mg/m², the incidence of clinically significant cardiac dysfunction was low. Of the 418 patients treated with Caelyx 50 mg/m²/cycle, and having a baseline measurement of left ventricular ejection fraction (LVEF) and at least one follow-up measurement assessed by MUGA scan, 88 patients had a cumulative anthracycline dose of >400 mg/m², an exposure level associated with an increased risk of cardiovascular toxicity with conventional doxorubicin. Only 13 of these 88 patients (15%) had at least one clinically significant change in their LVEF, defined as an LVEF value less than 45% or a decrease of at least 20 points from baseline. Furthermore, only 1 patient (cumulative anthracycline dose of 944 mg/m²), discontinued study treatment because of clinical symptoms of congestive heart failure.

As with other DNA-damaging antineoplastic agents, secondary acute myeloid leukemias and myelodysplasias have been reported in patients having received combined treatment with doxorubicin. Therefore, any patient treated with doxorubicin should be kept under haematological supervision.

Although local necrosis following extravasation has been reported very rarely, Caelyx is considered to be an irritant. Animal studies indicate that administration of doxorubicin hydrochloride as a liposomal formulation reduces the potential for extravasation injury. If any signs or symptoms of extravasation occur (e.g., stinging, erythema) terminate the infusion

immediately and restart in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Caelyx must not be given by the intramuscular or subcutaneous route.

Recall of skin reaction due to prior radiotherapy has rarely occurred with Caelyx administration.

Following the marketing of Caelyx, serious skin conditions including erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis have been reported very rarely.

In patients treated with Caelyx, cases of venous thromboembolism, including thrombophlebitis, venous thrombosis and pulmonary embolism have been seen uncommonly. However, because patients with cancer are at increased risk for thromboembolic disease, a causal relationship cannot be determined.

4.9 Overdose

Acute overdosing with doxorubicin hydrochloride worsens the toxic effects of mucositis, leukopaenia and thrombocytopaenia. Treatment of acute overdose of the severely myelosuppressed patient consists of hospitalisation, antibiotics, platelet and granulocyte transfusions and symptomatic treatment of mucositis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytotoxic agents (anthracyclines and related substances), ATC code: L01DB.

The active ingredient of Caelyx is doxorubicin hydrochloride, a cytotoxic anthracycline antibiotic obtained from *Streptomyces peucetius* var. *caesius*. The exact mechanism of the antitumour activity of doxorubicin is not known. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for the majority of the cytotoxic effects. This is probably the result of intercalation of the anthracycline between adjacent base pairs of the DNA double helix thus preventing their unwinding for replication.

A phase III randomized study of Caelyx versus doxorubicin in patients with metastatic breast cancer was completed in 509 patients. The protocol-specified objective of demonstrating non-inferiority between Caelyx and doxorubicin was met, the hazard ratio (HR) for progression-free survival (PFS) was 1.00 (95% CI for HR=0.82 - 1.22). The treatment HR for PFS when adjusted for prognostic variables was consistent with PFS for the ITT population.

The primary analysis of cardiac toxicity showed the risk of developing a cardiac event as a function of cumulative anthracycline dose was significantly lower with Caelyx than with doxorubicin (HR=3.16, $p < 0.001$). At cumulative doses greater than 450 mg/m² there were no cardiac events with Caelyx.

A phase III comparative study of Caelyx versus topotecan in patients with epithelial ovarian cancer following the failure of first-line, platinum based chemotherapy was completed in 474 patients. There was a benefit in overall survival (OS) for Caelyx-treated patients over topotecan-treated patients as indicated by a hazard ratio (HR) of 1.216 (95% CI; 1.000, 1.478), p=0.050. The survival rates at 1, 2 and 3 years were 56.3%, 34.7% and 20.2% respectively on Caelyx, compared to 54.0%, 23.6% and 13.2% on topotecan.

For the sub-group of patients with platinum-sensitive disease the difference was greater: HR of 1.432 (95% CI; 1.066, 1.923), p=0.017. The survival rates at 1, 2 and 3 years were 74.1%, 51.2% and 28.4% respectively on Caelyx, compared to 66.2%, 31.0% and 17.5% on topotecan.

The treatments were similar in the sub-group of patients with platinum refractory disease: HR of 1.069 (95% CI; 0.823, 1.387), p=0.618. The survival rates at 1, 2 and 3 years were 41.5%, 21.1% and 13.8% respectively on Caelyx, compared to 43.2%, 17.2% and 9.5% on topotecan.

A phase III randomized, parallel-group, open-label, multicentre study comparing the safety and efficacy of Caelyx plus bortezomib combination therapy with bortezomib monotherapy in patients with multiple myeloma who have received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy, was conducted in 646 patients. There was a significant improvement in the primary endpoint of time to progression (TTP) for patients treated with combination therapy of Caelyx plus bortezomib compared to patients treated with bortezomib monotherapy as indicated by a risk reduction (RR) of 35% (95% CI; 21-47%), p <0.0001, based on 407 TTP events. The median TTP was 6.9 months for the bortezomib monotherapy patients compared with 8.9 months for the Caelyx plus bortezomib combination therapy patients. A protocol-defined interim analysis (based on 249 TTP events) triggered early study termination for efficacy. This interim analysis showed a TTP risk reduction of 45% (95% CI; 29-57%), p <0.0001. The median TTP was 6.5 months for the bortezomib monotherapy patients compared with 9.3 months for the Caelyx plus bortezomib combination therapy patients. These results, though not mature, constituted the protocol defined final analysis.

5.2 Pharmacokinetic properties

Caelyx is a long-circulating pegylated liposomal formulation of doxorubicin hydrochloride. Pegylated liposomes contain surface-grafted segments of the hydrophilic polymer methoxypolyethylene glycol (MPEG). These linear MPEG groups extend from the liposome surface creating a protective coating that reduces interactions between the lipid bilayer membrane and the plasma components. This allows the Caelyx liposomes to circulate for prolonged periods in the blood stream. Pegylated liposomes are small enough (average diameter of approximately 100 nm) to pass intact (extravasate) through defective blood vessels supplying tumours. Evidence of penetration of pegylated liposomes from blood vessels and their entry and accumulation in tumours has been seen in mice with C-26 colon carcinoma tumours and in transgenic mice with KS-like lesions. The pegylated liposomes also have a low permeability lipid matrix and internal aqueous buffer system that combine to keep doxorubicin hydrochloride encapsulated during liposome residence time in circulation.

The plasma pharmacokinetics of Caelyx in humans differ significantly from those reported in the literature for standard doxorubicin hydrochloride preparations. At lower doses (10 mg/m² – 20 mg/m²) Caelyx displayed linear pharmacokinetics. Over the dose range of 10 mg/m² – 60 mg/m² Caelyx displayed non-linear pharmacokinetics. Standard doxorubicin hydrochloride displays extensive tissue distribution (volume of distribution: 700 to 1,100 l/m²) and a rapid elimination clearance (24 to 73 l/h/m²). In contrast, the pharmacokinetic profile of Caelyx indicates that Caelyx is confined mostly to the vascular fluid volume and that the clearance of doxorubicin from the blood is dependent upon the liposomal carrier. Doxorubicin becomes available after the liposomes are extra-vasated and enter the tissue compartment.

At equivalent doses, the plasma concentration and AUC values of Caelyx which represent mostly pegylated liposomal doxorubicin hydrochloride (containing 90% to 95% of the measured doxorubicin) are significantly higher than those achieved with standard doxorubicin hydrochloride preparations.

Caelyx should not be used interchangeably with other formulations of doxorubicin hydrochloride.

Population pharmacokinetics

The pharmacokinetics of Caelyx was evaluated in 120 patients from 10 different clinical trials using the population pharmacokinetic approach. The pharmacokinetics of Caelyx over the dose range of 10 mg/m² to 60 mg/m² was best described by a two compartment non-linear model with zero order input and Michaelis-Menten elimination. The mean intrinsic clearance of Caelyx was 0.030 l/h/m² (range 0.008 to 0.152 l/h/m²) and the mean central volume of distribution was 1.93 l/m² (range 0.96 – 3.85 l/m²) approximating the plasma volume. The apparent half-life ranged from 24 – 231 hours, with a mean of 73.9 hours.

Breast cancer patients

The pharmacokinetics of Caelyx determined in 18 patients with breast carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.016 l/h/m² (range 0.008 - 0.027 l/h/m²), the mean central volume of distribution was 1.46 l/m² (range 1.10 - 1.64 l/m²). The mean apparent half-life was 71.5 hours (range 45.2 - 98.5 hours).

Ovarian cancer patients

The pharmacokinetics of Caelyx determined in 11 patients with ovarian carcinoma were similar to the pharmacokinetics determined in the larger population of 120 patients with various cancers. The mean intrinsic clearance was 0.021 l/h/m² (range 0.009 – 0.041 l/h/m²), the mean central volume of distribution was 1.95 l/m² (range 1.67 – 2.40 l/m²). The mean apparent half-life was 75.0 hours (range 36.1 – 125 hours).

AIDS-KS patients

The plasma pharmacokinetics of Caelyx were evaluated in 23 patients with KS who received single doses of 20 mg/m² administered by a 30-minute infusion. The pharmacokinetic parameters of Caelyx (primarily representing pegylated liposomal doxorubicin hydrochloride and low levels of unencapsulated doxorubicin hydrochloride) observed after the 20 mg/m² doses are presented in Table 17.

Table 17 Pharmacokinetic Parameters in Caelyx-Treated AIDS-KS Patients

Parameter	Mean + Standard Error 20 mg/m² (n=23)
Maximum Plasma Concentration* (μg/ml)	8.34 ± 0.49
Plasma Clearance (l/h/m²)	0.041 ± 0.004
Volume of Distribution (l/m²)	2.72 ± 0.120
AUC (μg/ml h)	590.00 ± 58.7
λ_1 half-life (hours)	5.2 ± 1.4
λ_2 half-life (hours)	55.0 ± 4.8

5.3 Preclinical safety data

In repeat dose studies conducted in animals, the toxicity profile of Caelyx appears very similar to that reported in humans who receive long-term infusions of standard doxorubicin hydrochloride. With Caelyx, the encapsulation of doxorubicin hydrochloride in pegylated liposomes results in these effects having a differing strength, as follows.

Cardiotoxicity: Studies in rabbits have shown that the cardiotoxicity of Caelyx is reduced compared with conventional doxorubicin hydrochloride preparations.

Dermal toxicity: In studies performed after the repeated administration of Caelyx to rats and dogs, serious dermal inflammations and ulcer formations were observed at clinically relevant dosages. In the study in dogs, the occurrence and severity of these lesions was reduced by lowering the dose or prolonging the intervals between doses. Similar dermal lesions, which are described as palmar-plantar erythrodysesthesia were also observed in patients after long-term intravenous infusion (see Section 4.8).

Anaphylactoid response: During repeat dose toxicology studies in dogs, an acute response characterised by hypotension, pale mucous membranes, salivation, emesis and periods of hyperactivity followed by hypoactivity and lethargy was observed following administration of pegylated liposomes (placebo). A similar, but less severe response was also noted in dogs treated with Caelyx and standard doxorubicin.

The hypotensive response was reduced in magnitude by pretreatment with antihistamines. However, the response was not life-threatening and the dogs recovered quickly upon discontinuation of treatment.

Local toxicity: Subcutaneous tolerance studies indicate that Caelyx, as against standard doxorubicin hydrochloride, causes slighter local irritation or damage to the tissue after a possible extravasation.

Mutagenicity and carcinogenicity: Although no studies have been conducted with Caelyx, doxorubicin hydrochloride, the pharmacologically active ingredient of Caelyx, is mutagenic and carcinogenic. Pegylated placebo liposomes are neither mutagenic nor genotoxic.

Reproductive toxicity: Caelyx resulted in mild to moderate ovarian and testicular atrophy in mice after a single dose of 36 mg/kg. Decreased testicular weights and hypospermia were present in rats after repeat doses 0.25 mg/kg/day and diffuse degeneration of the seminiferous tubules and a marked decrease in spermatogenesis were observed in dogs after repeat doses of 1 mg/kg/day (see Section 4.6).

Nephrotoxicity: A study has shown that Caelyx at a single intravenous dose of over twice the clinical dose produces renal toxicity in monkeys. Renal toxicity has been observed with even lower single doses of doxorubicin HCl in rats and rabbits. Since an evaluation of the post-marketing safety database for Caelyx in patients has not suggested a significant nephrotoxicity liability of Caelyx, these findings in monkeys may not have relevance to patient risk assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

%-(2-[1,2-distearoyl-*sn*-glycero(3) phosphooxy]ethylcarbamoyl)-&-methoxypoly(oxyethylen)-40 sodium salt (MPEG-DSPE)

- fully hydrogenated soy phosphatidylcholine (HSPC)
- cholesterol
- ammonium sulphate
- sucrose
- histidine
- water for injections
- hydrochloric acid

- sodium hydroxide

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 Shelf life

20 months

After dilution:

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.
- From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.
- Partially used vials must be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).

Do not freeze.

For storage conditions of the diluted medicinal product, see Section 6.3

6.5 Nature and contents of container

Type I glass vials, each with a siliconised grey bromobutyl stopper, and an aluminium seal, with a deliverable volume of 10 ml (20 mg) or 25 ml (50 mg).

Caelyx is supplied as a single pack or packs of ten vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Do not use material that shows evidence of precipitation or any other particulate matter.

Caution must be exercised in handling Caelyx solution. The use of gloves is required. If Caelyx comes into contact with skin or mucosa, wash immediately and thoroughly with soap and water. Caelyx must be handled and disposed of in a manner consistent with that of other anticancer medicinal products in accordance with local requirements.

Determine the dose of Caelyx to be administered (based upon the recommended dose and the patient's body surface area). Take the appropriate volume of Caelyx up into a sterile syringe. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in Caelyx. The appropriate dose of Caelyx must be diluted in 5% (50 mg/ml) glucose solution for infusion prior to administration. For doses <90 mg, dilute Caelyx in 250 ml, and for doses 90 mg, dilute Caelyx in 500 ml. This can be infused over 60 or 90 minutes as detailed in 4.2.

The use of any diluent other than 5% (50 mg/ml) glucose solution for infusion, or the presence of any bacteriostatic agent such as benzyl alcohol may cause precipitation of Caelyx.

It is recommended that the Caelyx infusion line be connected through the side port of an intravenous infusion of 5% (50 mg/ml) glucose. Infusion may be given through a peripheral vein. Do not use with in-line filters.

7. MARKETING AUTHORISATION HOLDER

[redacted]

Belgium

8. MARKETING AUTHORISATION NUMBER(S)

[redacted]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: [redacted]

Date of last renewal: [redacted]

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines. http://www.emea.europa.eu/