SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 30 November 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

The initial approved indication for Caelyx was the treatment of Kaposi's sarcoma (KS) in patients with human immunodeficiency syndrome (AIDS). 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 doxorubicin (or other anthracycline). Early in the acquired immunodeficiency syndrome (AIDS) epidemic, KS was the most frequent opportunistic neoplasm encountered in patients with AIDS. Due to major improvement of antiviral treatment the prevalence of KS has markedly decreased and KS is now occurring later in the course of HIV infection, in advanced AIDS patients with low CD4 cell count. Complications of AIDS-related KS depend primarily on the stage of the disease and its pattern of clinical manifestations: cutaneous versus visceral.
In 2000 the indication was extended to include the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.
Caelyx contains the active substance doxorubicin hydrochloride (HCl), an anthracycline antibiotic, which inhibits cell proliferation by interaction with nucleic acid.
Caelyx consists of a liposomal formulation of doxorubicin HCl encapsulated in a delivery system of long circulating liposomes (Stealth® or sterically stabilised liposomes) with surface-bound methoxy-polyethylene glycol distearoylphosphoethanolamine sodium salt (MPEG-DSPE). This process is known as pegylation and protects liposomes from detection by the mononuclear phagocyte system, which increases blood circulation time. Caelyx is therefore characterised by long-acting properties.
Caelyx is a concentrate for infusion supplied in strength 2 mg/ml and presented as a sterile, translucent, red suspension after dilution in a solution of glucose for intravenous infusion.

2. Chemical, pharmaceutical and biological aspects

The information related to the active substance, doxorubicin HCl obtained from *Streptomyces peucetius* var. *caesius* and submitted in this application constitute the open part of the Drug Master File (DMF) as prepared by the supplier of doxorubicin HCl. However, the full documentation including in the DMF has already been evaluated by the UK Authorities in relation to another application and has been found satisfactory.
For the finished medicinal product, three formulations have been developed. The one intended to be put on the market includes ammonium sulphate (drug loading related to the concentration) and three lipid components which constitute the liposomal membrane:

- Fully hydrogenated soy phosphatidyl choline (HSPC)
- α-(2-[1,2-distearoyl-sn-glycero(3)phosphooxy]ethylcarbamoyl)-ω-methoxypoly(oxyethylen)-40, sodium salt (MPEG-DSPE)
- Cholesterol.

To ensure that there is no risk of transmission of bovine spongiform encephalopathy linked to the use of cholesterol, the applicant provided information on the source of this material.
As MPEG-DSPE, an amphophilic compound responsible for the long acting properties of these liposomes, is a new critical excipient, full documentation has been submitted. With regards to its function in this formulation, the most important feature of this molecule is the hydrophilic-lipophilic balance (HLB) essential for proper disposition between the lipophilic regions of the liposome surface and the aqueous surrounding region. Plasma circulation times for these liposomes are sensitive to changes in the hydrophilic shell provided by MPEG-DSPE i.e. related to the molecular weight of the MPEG used. With MPEG 2,000 and above, satisfactory prolongation is observed. Therefore to

reassure that a small reduction would not have a significant effect on liposomal circulation times the applicant agreed to tighten the molecular weight specification for MPEG-DSPE.
The complicated manufacturing process was considered to be well-described in the application. The actual formation of the liposomes is standard. The manufacturing process involves a sterile filtration step using a filter that has been validated. Bulk holding times have been minimised or eliminated to control potential microbial contamination. In response to a concern raised with respect to microbial contamination, a pre-sterilised bioburden limit was adopted by the applicant above which batches will be rejected.
In relation to the finished product specifications at release and at the end of shelf-life, the applicant agreed to tighten some specifications to improve the consistency and the uniformity of the medicinal product and to reassure that changes in product quality during storage do not affect clinical performance.
The container is in compliance with the European Pharmacopoeia: Type I clear glass vial with a bromobutyl rubber stopper (siliconised).
Results of stability tests are considered consistent to support the proposed shelf life of 18 months. Therefore, a shelf-life of 18 months is appropriate when the finished product is stored in the original container between 2° and 8°C. In relation to the diluted product, data indicate adequate stability in dextrose 5% for no more than 24 hours at temperatures between 2° and 8°C.
In summary, pharmaceutical issues, which have been raised during the evaluation of the application, have been resolved and all the data provided gave the assurance of the quality of the medicinal product.
In the course of the extension of the indication to ovarian cancer the MAH applied for an additional pack-size to accommodate the higher dose for the new indication .(50mg/25ml). The stability data provided demonstrated that the new 50 mg vials are of comparable quality to the initial 20 mg vials and support an identical shelf life.

3. Toxico-pharmacological aspects

Doxorubicin HCl is an anticancer anthracycline antibiotic. It acts through intercalation of bases of double-stranded DNA, and by inhibition of DNA topoisomerase II, an enzyme involved in DNA replication, whose activity is markedly increased in proliferating cells.
Caelyx accumulates in areas of abnormal vessel architecture commonly observed in malignant tumours. Since KS is a highly vascularised tumour, it is expected that Caelyx will preferentially accumulate in KS lesions.
During the development programme, three formulations of Caelyx were evaluated. To simplify the assessment, only data related to the formulation intended to be introduced onto the market are considered in this document.

Pharmacodynamics
Studies on pharmacodynamic effects with respect to the proposed indication have been performed *in vivo* in mice using a range of murine and human xenograft tumour types. Results showed that in a variety of tumour models, Caelyx was more effective than the same dose of doxorubicin hydrochloride in inhibiting tumour growth, in effecting cures and/or prolonging survival. Variation in liposomal diameter in the range 100-150 nm had no significant effect on anti-tumour activity of Caelyx. As part of the indication is in patients refractory to conventional chemotherapy, the Multi-Drug Resistance (MDR) has been estimated. Since some preliminary investigations on the activity of Caelyx in MDR tumour model suggest that this medicinal product can overcome MDR to some extent, and since no evidence for MDR was observed in patients who failed prior anthracyclines, MDR is considered unlikely to be a major problem with Caelyx.
Studies intended to investigate potential secondary pharmacological effects of the stealth placebo liposomes (i.e. “empty” liposome containing no doxorubicin hydrochloride) revealed no neurotoxicity signs or adverse behavioural effects in rodents. In a non-rodent, after an i.v. infusion of stealth placebo liposomes, hypotensive effects characterised as anaphylactic-like responses were reported. The relevance of this effect to the clinical use of Caelyx is unknown. However, to reflect this observation, a statement has been included in the SPC. *In vitro*, Caelyx, stealth placebo liposomes and free doxorubicin appeared to have minimal haemolytic effect when mixed with human or rodent blood.

Sufficient data from animal models were provided to demonstrate the anti-tumour activity of Caelyx to a range of murine and human xenograft tumour types.

Pharmacokinetics

Although the ADME studies (absorption, distribution, metabolism and excretion), and in particularly metabolism and excretion components, carried out in rats, rabbits and dogs, were considered sparse, data were available to characterise the major differences and similarities between free doxorubicin HCl and this liposomal formulation.

The pharmacokinetic profile of Caelyx, determined in multiple species was considered well characterised. After a single intravenous (IV) administration, the volume of distribution was shown to be approximate to the total blood volume, which indicated low liposome uptake by normal tissues in comparison with free doxorubicin HCl. The principal pharmacokinetic characteristics are biphasic plasma concentration-time curve, low rate of clearance, high area-under-the-curve (AUC), small volume of distribution and a prolonged secondary half-life that accounts for the majority (> 95%) of the AUC. Regarding metabolism, some results have demonstrated that liposomal incorporation modifies the pharmacokinetics and tissue distribution of doxorubicin without any major effect on the route of metabolism.

Multiple-dose studies in rodents and non-rodents gave dose-proportional tissue concentrations of doxorubicin with distribution patterns comparable to those in the single-dose rodent study. Caelyx produced lower tissue levels of doxorubicin in heart and kidney compared with equimolar doses of doxorubicin HCl. Skin lesions noted in both rodents and non-rodents were associated with higher drug concentrations compared with those in unaffected skin.

No relationship has been found between tissue AUCs (free + liposomal doxorubicin) and toxicity in animal studies conducted with Caelyx. To explain this , two hypotheses, considered satisfactory have been suggested, based on the relationship of toxicity to peak doxorubicin HCl concentration and on the lymphatic drainage of normal tissues.

A single-dose study in rodents showed that pharmacokinetic parameters are independent of minor variations in lipid composition, liposome particle size, content of LPC or source of MPEG-DSPE.

No further distribution and excretion studies using stealth placebo liposomes have been performed.

The main pharmacokinetic characteristics of Caelyx are the extended half-life and the higher C_{max} and AUC values in comparison to conventional doxorubicin injection at equimolar doses.

Toxicology

A repeated-dose intravenous toxicity study undertaken in rodents with Caelyx was discontinued after eight doses owing to high mortality related to skin toxicity and poor general health of the animals. Similar toxic effects were observed for Caelyx and doxorubicin HCl: decreased body weight, decreased white blood cells (WBC) and red blood cells (RBC) counts, thymic and testicular atrophy, hypocellular bone marrow, myocyte vacuolation and myocardial degeneration. Caelyx was less myelotoxic, cardiotoxic and nephrotoxic than doxorubicin HCl, but more dermotoxic (reversible dermal toxicity in the form of lesions on the feet and legs). A study performed in a non-rodent species led to the same conclusions. In terms of dermal toxicity, the no-effect level was 0.25 mg/kg in both rodent and non-rodent species.

Two additional studies, one in a non-rodent species, have been undertaken to assess the cardiac, haematological and dermal toxicity of Caelyx. In an animal model for anthracycline cardiotoxicity, up to 50% more Caelyx than doxorubicin could be administered without incurring an increased risk of cardiomyopathy. In a non-rodent species, the severity of Caelyx-associated dermal lesions is related to dose and dosing interval, with lower doses or longer dosing intervals resulting in reduced lesion severity.

Myelosuppression was mild and appeared to be primarily confined to the erythroid series. The dermal lesions were generally a more important dose-limiting parameter than myelotoxicity for Caelyx which is not the case for doxorubicin HCl.

The toxicology programme is not complete in relation to reproductive toxicity and mutagenicity. The genotoxicity of Caelyx as a finished product has not been evaluated since doxorubicin, as a powerful mutagen would have swamped any response from the stealth placebo liposomes. Therefore, only the genotoxic potential of the liposomes has been evaluated in a conventional package of tests. Results obtained confirm the innocuity of the liposome components.

The evaluation of reproductive toxicity was restricted to fertility studies (segment II). Since there are data on the embryotoxic and teratogenic nature of doxorubicin HCl, as well as on its ability to induce long-term or permanent sterility (in rats and dogs testicular atrophy may be observed), it was considered acceptable not to repeat the studies with Caelyx. The administration of high doses of Caelyx to pregnant rodent species was associated with decreased foetal weights, decreased litter size and increased resorptions. In a non-rodent species, Caelyx was revealed to be abortifacient. In relation to these data, appropriate comments have been included in the Summary of Product Characteristics (SPC).
A local tolerance study, performed in a non-rodent species receiving Caelyx by IV injection revealed no treatment-related injection-site intolerance. However, after subcutaneous administration, dose-dependent inflammatory reactions have been observed indicating that Caelyx may provoke an inflammatory response after accidental perivenous administration. To reflect this fact, appropriate recommendations and precautions have been added in the SPC. Data on the haemolytic potential of Caelyx submitted showed that neither Caelyx nor the "empty" liposomes caused any haemolysis of human RBCs or any coagulation or precipitation of human serum or plasma.
The toxicity of MPEG-DSPE, one of the three lipid components of the stealth liposome, has only been evaluated through a limited single-dose study carried out in mice. Nevertheless, results indicate that the material is not acutely toxic.
In conclusion, although Caelyx and doxorubicin HCl present a similar toxicity profile, Caelyx produces more dermal lesions primarily on the feet and legs whereas doxorubicin HCl is more cardiotoxic and nephrotoxic. The toxicity profile of Caelyx has been well defined based on available literature data on conventional doxorubicin HCl and results from adequate studies performed in relation to the indication claimed and population sought.

4. Clinical aspects

Kaposis's sarcoma
Although Kaposi's sarcoma (KS) is generally not life- threatening with the exception of gastrointestinal and pulmonary KS, the disease can be severely debilitating (e.g. debilitating oedema, pain, facial oedema, dyspnea). AIDS-KS classification is based upon patient's overall clinical and immunological status as well as the therapeutic goals of the treatment (AIDS Clinical Trials Group (ACTG) classification using the Tumour-Immune-System-Systemic illness staging criteria, distribution of KS lesion sites and overall number of lesions). Current palliative systemic therapies available are:

- alpha-interferon indicated for treatment of patients with AIDS-KS that have no history of opportunistic infections and have relatively intact immune systems, i.e., patients with CD4 counts ≥ 200 mm^3.
- cytotoxic chemotherapy such as bleomycin and vincristine (BV) or doxorubicin HCl, bleomycin and vincristine (ABV). The latest combinations are commonly used although none of these medicinal products is licensed for treatment of AIDS-KS.

The objective of a liposomal formulation is to allow the release of doxorubicin HCl preferentially at KS lesions and minimise sites of toxicity.
Caelyx is intended to be administered intravenously at 20 mg/m^2 every two to three weeks for the treatment of AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm^3) 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 doxorubicin (or other anthracycline).

Pharmacodynamics and pharmacokinetics
Since the active moiety is well known, no human pharmacodynamic studies specific for this formulation have been performed.
The recommended dosing regimen (20 mg/m^2 every two to three weeks) is based on results obtained from two studies which identified the maximum tolerated dose in the intended patient population. Of the three doses tested (10 mg/m^2, 20 mg/m^2 and 40 mg/m^2), 40 mg/m^2 provoked an unacceptable level

of myelosuppression in AIDS-KS patients and there was evidence that 20 mg/m^2 is more effective than 10 mg/m^2.
These data were considered sufficient since they are in line with current recommendations introduced in ICH and CPMP guidelines.
The pharmacokinetic behaviour of Caelyx has been established in cancer patients with solid tumours and in AIDS patients with KS through three studies although only one study (randomised, crossover of single dose of Caelyx 10 or 20 mg/m^2 separated by 3 week washout period and involving 43 patients) was conducted in the indicated patient population with the final formulation intended to be on the market.
Caelyx displays linear pharmacokinetics as AUC and C_{max} appeared dose related. In addition Caelyx presents a bicompartmental pharmacokinetics with an initial half-life of approximately 5 hours, which accounts for less than 5% of the total AUC, and a secondary phase of 55 hours which represents the remainder of the AUC.
Compared to Caelyx, free-doxorubicin HCl is cleared rapidly from the plasma, with an initial half-life of approximately 10 minutes, reflecting the rapid tissue uptake of doxorubicin. The apparent volume of distribution of Caelyx is approximately equal to the estimated plasma volume, which suggests that encapsulated drug is restricted from entering the extravascular compartment during the plasma distribution phase. At 20 mg/m^2, the measured ratios between lesion and normal skin, determinated following collection of biopsy and plasma samples, indicate that Caelyx, therefore, preferentially accumulates in KS lesions.
Clearance (Cl_t) is prolonged compared to conventional doxorubicin HCl.
After intravenous administration, doxorubicin HCl is rapidly metabolised primarily in its major metabolite, doxorubicinol. It has been demonstrated that liposome encapsulated doxorubicin can not be metabolised, thus the amount of doxorubicinol in plasma is derived from metabolism of doxorubicin that has been released from the liposome. However, based on the results of a physiologically based pharmacokinetic simulation model and plasma levels of doxorubicinol measured throughout this study, the level of free doxorubicin released from the liposome has been determined as very low.
The recommended dose interval for Caelyx is longer than the interval required to avoid accumulation (around 5 half-lives). The clearance half-life of conventional doxorubicin HCl (approximately 10 minutes in humans) and results obtained from preclinical studies justified the absence of a study evaluating the potential accumulation.
The potential of interactions with parenteral, nutritional lipid-solutions, or other liposomal products has not been studied. However, such an interaction is not expected owing to the physical characteristics on the stealth liposome.
An ongoing clinical study evaluates the pharmacokinetics of Caelyx in hepatic cancer patients as determinated by pre-study total bilirubin concentrations. The pharmacokinetic parameters (clearance, half-lives) for these patients appear to be similar to the pharmacokinetic parameters for the 41 AIDS-KS patients from the randomised cross-over single dose pharmacokinetic study. When both populations are combined by initial bilirubin level, there still appears no difference in the clearance or half-lives. These data suggest therefore that the pharmacokinetics of Caelyx are unaffected by hepatic insufficiency. However, because of the small number of patients involved and the lack of clinical experience, information which recommends to reduce dosage based on experience gained with conventional doxorubicin has been included in the SPC.
Concerning renally impaired patients, no studies have been carried out. However, based on the fact that doxorubicin is both metabolised by the liver and excreted by the bile, it was considered reasonable that no dose adjustment is required with Caelyx for this subpopulation group, as reflected in the SPC.
In summary, the general pharmacokinetic profile of Caelyx is known and confirms that stealth coating allows liposomes containing doxorubicin HCl to circulate for prolonged periods of time in the plasma of AIDS-KS patients. The liposomes may be more concentrated in KS lesions where the substance-loaded is released. Nevertheless it should be kept in mind that there are limited data regarding metabolism and excretion of Caelyx, pharmacokinetic profile in special population groups and drug-drug interaction, especially with other chemotherapies.

Efficacy
The initial clinical development programme consisted of two uncontrolled open pivotal studies. These studies involved comparable patient populations (nearly exclusively white homosexual males, aged on

average 38 years, with advanced AIDS and extensive KS as reflected in the low CD4 cells count, high percentage of patients at poor risk using the AIDS Clinical Trial Group). Patients enrolled were considered as being representative of the overall patient population with AIDS-related Kaposi's sarcoma.
This first study involving 247 patients was designed as a multicentre, uncontrolled open trial of Caelyx. The median dose received was 20 mg/m^2 and patients received a total of 2,015 cycles of treatment, cycles being repeated at 2 weekly intervals. Clinical endpoints included therapeutic response and Quality of Life. Results obtained from this study are as follows:

complete response	**6.3 %**
partial response	**74.4 %**
stable	**18.5 %**
progression	**0.8 %**

complete response (CR) defined as absence of any detectable residual disease
partial response (PR) defined as absence of new lesions (cutaneous - visceral)
stable disease (SD) defined as any response not meeting the criteria for CR, PR or PD
progressive disease (PD) defined as development of new events such as new lesions
Long-term follow-up is ongoing and only a portion of the patients received the intended marketed formulation. However, analysis of response on the basis of formulation administered did not show any significance in response data. To date, the mean duration of response is 117 days and quality of life data related to pain seem to be improved.

This second study involving 137 patients with AIDS related to KS was designed as an uncontrolled, open trial. The median dose of Caelyx final formulation was 20 mg/m^2, repeated 3 weekly.
793 cycles of therapy were administered with a median cumulative dose of 110 mg/m^2. Response rates were as follows:

complete response	**0 %**
partial response	**61.8 %**
stable	**26.5 %**
progression	**11.8 %**

Results obtained from this study were considered as encouraging in terms of response and reduction of pain in all patients included those who received previous chemotherapy. Median duration of response was 92 days. Effects on survival were not significant as 37 patients had died by the cut-off date.

To support the efficacy of Caelyx in patients who are either resistant to prior chemotherapy or intolerant to prior chemotherapy due to toxicity, data obtained from a cohort of 77 "refractory" patients within the study 30-12 have been submitted. These 77 patients received substantial prior therapy for KS, prior to enrolment in the study. Forty patients received local radiation therapy, thirty received intralesional injections of vinblastine and twenty received systemic treatment with alfa-interferon. Many patients received single agent chemotherapy and all patients received combination systemic chemotherapy comprising at least two of the following agents: a vinca alkaloid, bleomycin and doxorubicin (or other anthracycline). The % antitumour response in these patients was 57%.

The analysis of these two studies has been adjusted according to leucopenia, systemic illness (including prior opportunistic infection) and CD4 cell counts. It has been therefore demonstrated that the overall response rate for patients with initial neutropenia (ANC < 2000 cells/mm^3) is essentially the same (69.3%) as for patients with higher neutrophil counts at baseline (76.6%). In the same way, response rates are similar for patients with good risk (79%) and poor risk at baseline (68%) based on the extent of their systemic illness. With respect to CD4 counts, response rates are similar for patients with CD4 counts < 50 cells/mm^3 and CD4 counts > 50 cells/mm^3. However, 1% of patients with CD4 < 50 cells/mm^2 had a complete response against 10% of patients with highest CD4 counts.

It was suggested that data should be provided from randomised controlled studies in order to give adequate evidence of efficacy of Caelyx. Therefore the company submitted further data based on a prospectively randomised controlled, parallel, multicentre study of Caelyx (20 mg/m^2) versus ABV [Adriamycin (doxorubicin) (20 mg/m^2), bleomycin (10 U/m^2) and 1 mg vincristine] administered every 2 weeks for up to 6 cycles for Caelyx and for ABV. The study involved 258 patients with moderate to severe KS (patient demography: male 98%, Caucasian 75%, mean age 38 years, homosexual > 90%). Caelyx and ABV treatment arms involved 133 and 125 patients respectively. As for the studies mentioned above, most of the patients fell into a poor prognosis group.

The primary efficacy endpoint was based on the response rate to therapy (5 criteria: complete, clinical complete, partial response, stable and progressive disease) whereas the clinical benefit was judged on the basis of patient's assessment of lesion pain, the presence of signs and symptoms related to systemic lesions, Karnofsky performance status and two quality of life (QOL) questionnaires. One questionnaire for assessing QOL was disease-specific for AIDS-related KS and the other was developed by Wu utilising HIV-relevant items from the Medical Outcomes Study and validated by comparing patients with asymptomatic HIV infections and patients with AIDS-related complex.

A statistically significant difference in favour of Caelyx was demonstrated with respect to the complete/partial response rate at the end of the treatment (46% and 26% response rate for Caelyx and ABV respectively). Duration of response was similar in both groups (mean duration 92.5 days versus 84.8 days, median duration 90 versus 92 days for Caelyx and ABV respectively) as well as patient survival. The recording of lesion characteristics other than size, such as thickness, nodularity, oedema, colour and pain showed an improvement from baseline measurements for both studied groups. Death was not a study endpoint, but median survival was 160 days with Caelyx and 153 with ABV.

With respect to the QOL questionnaires, there were statistically significant differences in favour of Caelyx in 5/9 domains: general health, pain, social functioning, energy level and health distress. With respect to the KS-specific questionnaire, there were statistically significant differences in favour of Caelyx in 4/9 domains: pulmonary dysfunction/pain, restricted head/limb movement, exercise limitation and sleep disturbance.

In summary, this well-designed and well-conducted study showed equivalence and in some respects superiority of Caelyx compared to ABV in disease symptoms and cosmetic benefit. Although none of the components of ABV is licensed for the treatment of AIDS-KS, the choice of comparator is justified since it is currently recognised as an effective combination therapy for advanced AIDS-related KS.

As visceral KS affecting lungs is associated with a higher increase of death (48.6% of patients with KS in the lungs died on study compared to 33.9% of patients with other KS sites), a further evaluation of patients with such conditions in the three main studies indicated that doses and duration of treatment for subjects with lung involvement were not different from patients without lung involvement.

The active control study (30-11) designed as a randomised comparative trial of Caelyx versus bleomycin and vincristine (BV) confirmed the efficacy of C in the treatment of AIDS-related KS. The objectives of this trial were to determine the efficacy of Caelyx by comparison with an established therapy and to evaluate the safety and tolerance in a population of AIDS patients with moderate to severe KS.

A total of 241 patients with moderate to severe KS were involved, of whom 218 were evaluable for efficacy. Patients received intravenously either Caelyx administered at 20 mg/m^2 every three weeks or BV (15 mg/m^2 bleomycin and 1.4 mg/m^2 vincristine) administered in cycles every three weeks. The mean number of cycles per patient was 4.8 for Caelyx and 3.7 for BV. The primary endpoint was the therapeutic response defined as complete response, clinically complete response, partial response, stable and progression. The secondary endpoints included the patient's assessment of the lesion pain, the presence of signs and symptoms related to systemic lesions, Karnofsky performance status and two

Quality of Life (QoOL) questionnaires including one disease-specific for AIDS-related KS questionnaire. Results obtained from the study at the end of the treatment were as follows:

	CAELYX	BV
Complete response	0 %	0 %
Clinically complete response	3.3 %	0 %
Partial response	35.5 %	14.2 %
Stable	32.2 %	45.0 %
Progression	9.9 %	21.7 %

No patient showed complete response to either therapy.
A statistically significant difference ($p < 0.001$) in favour of Caelyx was demonstrated with regard to the clinically complete/partial response at the end of the treatment (38.8% and 14.2% response rate for Caelyx and BV respectively). The recording lesion characteristics (thickness, nodularity, oedema, colour, pain and size) showed a statistically significant improvement from baseline versus end of treatment in Caelyx group ($p < 0.006$). There was no statistically significant difference between Caelyx and BV in terms of change from baseline measurements in cutaneous and gastrointestinal lesion involvement by KS or in Karnofskyi performance status. With respect to the QoOL, there were statistically significant differences from baseline in favour of Caelyx in cognitive functioning and in difficulty wearing clothes.

Based on these results, Caelyx appeared to be effective in the treatment of AIDS-related KS in patients with low CD4 counts (< 200 CD4 cells/mm^3) and extensive mucocutaneous or visceral disease. A better compliance and a higher response rate is associated with Caelyx than with BV.

Safety
The safety profile of Caelyx was established based on results obtained from original data submitted, the comparative study with a second objective aimed to evaluate the safety and tolerance of Caelyx in comparison to ABV, from the AIDS-KS patient safety database updated to September 1995 including the follow-up of the second uncontrolled study which has since the end of 1994 become a compassionate use protocol. The second comparative trial (30-11) provided additional safety data.
With respect to results obtained from the first comparative study, Caelyx compared to ABV has been demonstrated to have a better tolerance since 68% of the patients completed the prescribed six cycles of treatment with this medicinal product against 34% with ABV. Data obtained from the comparative study support the fact that Caelyx is safer than conventional doxorubicin at the same dose in terms of myelotoxicity, cardiotoxicity, or other drug-related toxicities regardless of relationship to treatment (see table 1).

Table 1: Summary of safety data obtained from the comparative study

	Caelyx (n = 133)	ABV (n = 125)
Patients completing protocol	68 %	34 %
Hair loss	11 %	42 %
Severe neutropaenia (ANC < 500)	7 %	15 %
Mucositis/stomatitis	18 %	8 %
Nausea/vomiting	34 %	58 %
Peripheral neuropathy	12 %	28 %

Considering these results, patient tolerance on Caelyx appeared to be better than on ABV, since 68% of patients on Caelyx completed the protocol compared to 34.4% on ABV. Nausea/vomiting and peripheral neuropathy seemed to be less common with Caelyx, although the difference was not statistically significant. Although the overall incidence of neutropenia (ANC < 1000 cells/mm^3) was similar, patients treated with ABV experienced a significantly higher probability of developing severe neutropenia (ANC < 500 cells/mm^3) at sometime during the study than patients treated with Caelyx.

This higher level of neutropaenia was associated with a corresponding higher use of growth factors (G-CSF) in the ABV-treated patients.
In study 30-11, the two regimens did not show significant differences for most adverse events. However some events including allergic and anaphylactic reactions, gastrointestinal disturbances, confusion and dizziness were at least twice more frequent with Caelyx than with BV treatment.
Significantly more patients terminated early BV treatment than Caelyx due in particularly to adverse events (26.7% versus 10.7% respectively).
In this study opportunistic infections with three organisms (candidiasis, herpesx simplex and toxoplasmosis) were statistically significantly more frequent following Caelyx than following BV treatment. When adjusted for duration of exposure, the frequency of opportunistic infections is only slightly higher following Caelyx treatment which suggested that this difference might be due to a better compliance and longer exposure with the Caelyx regimen (median 160.0 days with Caelyx versus 62.5 days with BV). A higher frequency of leucopenia, possibly or probably associated to the drug was associated with Caelyx (71.9% versus 38.3% with BV).
So far, the overall treatment-related safety profile of Caelyx seemed to be favourable to Caelyx compared with the alternative combination therapy, since there are less risks associated with Caelyx and a better tolerability. However, in the comparative trial with the BV combination (Study 30-11) cases of opportunistic infections, anaphylaxis, confusion and dizziness have been highlighted.

Ovarian cancer
The pivotal trial 30-49 submitted in support of this indicationn was a Phase III open randomised comparative trial in women with advanced ovarian cancer who have failed a first-line platinum based chemotherapy regimen, with topotecan as the active comparator. In addition results from three Phase II studies were submitted.

Summary of Phase II studies
All three single arm trials targeted patients with recurrent ovarian carcinoma, with studies 30-47 and 30-47E including patients specifically refractory to both platinum and paclitaxel. All safety and efficacy analyses were based on the intent-to-treat (ITT) population. The dosing regimen was similar for all three studies: studies 47 and 47E prescribed a 50 mg/m^2 dose of Caelyx on a 4-week dosing interval whilst study 30- 22 prescribed a 3-week dosing interval.
The protocols used consistent definitions for evaluating response (the primary efficacy parameter). Responses were assessed by standard Southwest Oncology Group (SWOG) criteria, with confirmation four weeks later. Responses for study 30-22 and 30-47 underwent independent radiological review. The secondary efficacy parameters were time to response, duration of response and time to progression.
The overall response rate for the intent-to-treat population varied from 6.5% - 20% (Table 1). The overall response rate in the combined intent-to-treat population is 12.3%. The majority of patients experienced a partial response (25/27). The median time to progression varied from 81 to 172 days.

Table 1 Efficacy in the ITT population

Study	Efficacy parameters				
	Objective Response	Median Time to Response (days)	Median Duration of Response (days)	Median Time to Progression (days)	Median Overall Survival (days)
30-22	20%	167	427	172	376
30-47	13.1%	106	285	142	N/A
30-47E	6.5%	57	124	81	N/A

Data from the European 47E study showed a lower response rate than the US 47 study (6.5% vs 13.1%) and a shorter median time to progression (81 days versus 142 days). A detailed review of prior chemotherapy treatment revealed some significant differences between the studies. In particular more patients in study 47 had received paclitaxel combined with platinum as their first-line therapy than the patients in study 47E (75% vs 40%). It is recognised that the introduction of paclitaxel into first line therapy has a significant impact on overall survival in ovarian cancer and thus may explain these differences.

The MAH have provided further information on overall response rates in the platinum/paclitaxel refractory patients (14.5%) and in the platinum/paclitaxel/topotecan refractory population (9%). The combined refractory patients accounted for 188/219 ITT population.
However, the overall response rate of the combined refractory population is a modest 12.2%, very similar to the overall ITT cohort (12.3%).
Caelyx response rate based on prior platinum response was also evaluated. Patients who progress **during** their last platinum-containing regimen have a poorer prognosis than those who progress at a later time. This trend is also apparent in the refractory patients treated with Caelyx.

Phase III Study
The pivotal trial 30-49 was an open randomised comparative trial in women with advanced ovarian cancer who have failed a first-line platinum based chemotherapy regimen, with topotecan as the active comparator.
The final analysis includes 474 patients in the ITT population; 416 of these patients met protocol-specified enrolment criteria and received at least 2 cycles of study drug (evaluable population). 321/416 (77%) of the evaluable patients had received prior combination paclitaxel/platinum therapy. 439/474 (93%) of patients had progressed or died (217 Caelyx; 222 topotecan) and only 5/474 (1%) (4 Caelyx; 1 topotecan) were still being treated.

Efficacy
The primary endpoint was time to progression (TTP) for the evaluable population, with overall survival and response rate serving as secondary endpoints. Kaplan-Meier estimates of time to progression and overall survival were generated for both the evaluable and ITT populations and the treatment groups were compared using the stratified log-rank test. Hazard ratios for topotecan relative to Caelyx were calculated and protocol-specified 90% and interim analysis adjusted 91.6% confidence intervals were provided.
The MAH claims that whereas the study was designed to demonstrate non-inferiority, the results of the protocol-specified endpoint (time to progression in the evaluable population) demonstrate superiority of Caelyx over topotecan (hazard ratio 1.262, 90% CI 1.062-1.500, p=0.026). The results for the ITT population were similar but did not reach statistical significance. However, the study investigators were responsible for assigning treatment response, including radiographic response, and were not blinded to treatment assignment. Independent confirmation of the CT scans was not specified in the protocol and thus the risk of potential bias in assessment of the primary efficacy endpoint has not been adequately addressed. In addition, there are statistical concerns regarding the proportional hazards assumption. Therefore, a significant improvement in time to progression has not been established for Caelyx relative to topotecan.
Given the clinical and statistical reservations relating to the primary endpoint, overall survival would seem the better end-point to base conclusions upon, because overall survival is unaffected by any potential tumour assessment bias. Overall survival was similar for Caelyx and topotecan for both the evaluable and ITT populations, with the hazard ratio favouring Caelyx (HR 1.121, 90% CI 0.920-1.367, ITT population). As topotecan is an appropriate comparator, there is adequate evidence of the non-inferiority of Caelyx for the indication proposed**.**
Platinum sensitive and platinum refractory patients
Both time to progression and overall survival were significantly longer for Caelyx as compared to topotecan-treated patients in the platinum sensitive sub-group. Therefore, there is strong evidence of efficacy in patients with platinum-sensitive disease. In platinum refractory patients the survival trend favours topotecan (HR = 0.895, 90% CI 0.700 – 1.143). The evidence of non-inferiority is therefore less convincing in platinum refractory than in platinum sensitive patients. However, the distinction between these two platinum sub-groups is not a standardised one and in practice is only used when considering subsequent treatment with a platinum-containing regimen.

Safety and quality of life (QOL)
The median dose of Caelyx delivered was 50 mg/m^2, with a median cycle length of 30 days; median dose of topotecan delivered was 7 mg/m^2, with a median cycle length of 24 days. Most patients received 4 to 5 cycles of study drug.
Most patients discontinued the study drug due to disease progression: 48% for Caelyx and 47% for topotecan. Slightly more patients treated with Caelyx discontinued because of adverse events

(16% versus 12% of patients treated with topotecan). Overall, treatment-related adverse events observed with Caelyx tended to be of non-serious and of mild or moderate severity; however palmar-plantar erythrodysesthesia (PPE) was severe in 23% and stomatitis was severe in 8% of patients treated with Caelyx.
Both the incidence and severity of haematologic adverse events were greater with topotecan than with Caelyx. Neutropenia and anaemia were reported in 78% of the topotecan group compared to about 35% with Caelyx. Neutropenia was severe or life- threatening in 71% of topotecan-treated patients (including 2 deaths), compared with only 12% of Caelyx-treated patients. In addition, nausea and alopecia were more common with topotecan than with Caelyx.
Overall, the treatment impact on patients' health-related QOL was similar between the two treatments. QOL was assessed at week 12, and therefore data is only available on the 50% of patients who still remained in the study. Comparison of the groups in terms of maintenance of or improvement in scores from baseline to 12 weeks indicated a minor advantage in role/social functioning and global QOL scores for the Caelyx-treated group compared with the topotecan-treated group. However, topotecan-treated patients experienced significantly less pain than Caelyx-treated patients (81% versus 64% with maintenance of or improvement in pain scores) associated with an advantage in emotional functioning (74% versus 67%). PPE may have been responsible for the reported worsening of Pain score in the Caelyx-treated patients.
The global QOL was the same for platinum sensitive and refractory sub-groups, with 60% of patients reporting maintenance or improvement in global QOL scores at 12 weeks. Overall there appears to be adequate evidence of a favourable safety profile for Caelyx for the indication proposed. The benefit to risk balance of Caelyx seems comparable to that of topotecan in this indication.

5. Overall conclusion and benefit/risk assessment

Caelyx, a pegylated liposomal formulation of doxorubicin hydrochloride, was developed to provide effective palliative therapy for symptomatic AIDS-related Kaposi's sarcoma with an acceptable level of toxicity.
The chemical and pharmaceutical data were adequate to support the quality of this original liposomal formulation.
As the active substance is already well- known, the toxicological programme presented was considered sufficient.
Caelyx in the treatment of AIDS-KS patients is an effective palliative single agent therapy which has statistically significantly superior efficacy and tolerability compared with a current standard combination chemotherapy, ABV, which is an appropriate comparator in this particular patient population. Evidence of efficacy in refractory patients, has also been provided.
The CPMP has considered during the review process that, with regard to the data provided, the overall benefit/risk ratio for Caelyx is favourable for the proposed regimen in AIDS related KS and recommended granting a Marketing Authorisation for Caelyx for AIDS-related Kaposi's sarcoma (KS) in patients with low CD4 counts (< 200 CD4 lymphocytes/mm^3) and extensive mucocutaneous or visceral disease.
In a subsequent variation, data were provided regarding the efficacy and safety of Caelyx in patients with advanced ovarian cancer. The CPMP reviewed the submitted trials and considered that there is adequate evidence of a favourable benefit/risk ratio for Caelyx for the proposed indication: treatment of advanced ovarian cancer in women who have failed a first-line platinum based chemotherapy regimen. Whilst the evidence of non-inferiority is less convincing in platinum refractory than in platinum sensitive patients, the distinction between these two platinum sub-groups is not a standardised one and in practice is only used when considering subsequent treatment with a platinum-containing regimen.
Therefore, the CPMP recommended the extension to the Marketing Authorisation to include treatment of advanced ovarian cancer in women who have failed a first-line platinum based chemotherapy regimen.

6. Metastatic Breast Cancer

The indication of Caelyx was further extended in the area of the treatment of metastatic breast cancer. Tthe following two indications were initially applied for:

1 Metastatic breast cancer in women for whom an anthracycline would be considered.
2 Metastatic breast cancer in women who have failed a taxane containing regimen.

Following the evaluation of the dossier, the second indication was withdrawn by the MAH and the first was modified. The proposed posology was the same as for ovarian carcinoma and is as follows:

- Caelyx is administered intravenously at a dose of 50 mg/m^2 once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment

The safety profile of Caelyx differs from that of conventional doxorubicin formulations. In particular it is associated with palmar-plantar erythrodysesthesia (PPE), an adverse effect not generally seen with conventional doxorubicin formulations. PPE is characterised by a painful macular red skin eruption, particularly of the soles and palms. Allergic type infusion phenomena are also rather more frequent than with conventional doxorubicin formulations. Caelyx is, however, associated with less alopecia, nausea, vomiting and myelosuppression than equally effective doses of conventional doxorubicin. The question of its cardiotoxicity compared to conventional formulations in the setting of metastatic breast cancer was considered in this application.
Information was also proposed for inclusion into the SmPC which effectively claims that Caelyx is associated with less cardiotoxicity in this indication than conventional doxorubicin formulations.
In addition, the pharmacokinetics of doxorubicin differ when administered as *Caelyx.* Distribution is largely confined to the plasma compartment and the mean half life is much prolonged (73.8 hours) in comparison to conventional doxorubicin formulations.

- Clinical aspects

Three relevant studies were provided to support the application. These comprised one dose-finding breast cancer trial and two phase III studies conducted in subjects with metastatic breast cancer.

- **Study 30-17**, a dose-finding trial in altogether 73 patients with breast cancer.
- **Protocol I97-328**, a Phase III, randomised, comparative trial that compared the efficacy and cardiac safety of Caelyx to that of conventional doxorubicin in the first-line treatment of metastatic breast cancer
- **Protocol C/I96-352**, a Phase III, randomised, comparative study that compared the efficacy and safety of Caelyx with an approved salvage regimen (vinorelbine or mitomycin C + vinblastine) in women with advanced breast cancer who had failed a taxane-containing regimen.

Pharmacokinetics.
Population PK data were provided for 18 breast cancer patients for whom data are available. The kinetics of Caelyx in those with breast cancer appears similar to those with other tumours.

Dose- finding study
Study (**30-17**) was presented to justify the choice of dose. 73 patients were recruited who had either previously received no previous chemotherapy or, alternatively, had received cyclophosphamide and 5-Fluorouracil. The following dose schedules of Caelyx were assessed: 60mg/m^2 every 21 days, 45mg/m^2 every 28 days, 45mg/m^2 every 21 days, 60mg/m^2 every 28 days for two cycles followed by 45mg/m^2 every 28 days.
The dose regimen of 45mg/m^2 every 4 weeks was considered the optimal one of those studied. The dosage employed for the subsequent phase III trials was similar, 50 mg/m^2 every 4 weeks, which is also the approved dosage of Caelyx for the treatment of advanced ovarian cancer.

Efficacy in first line treatment

Phase III open label study **I97-328** compared Caelyx to conventional doxorubicin.

Methods

The protocol of the study is summarised in table 1:

Table 1. Protocol I97-328 outline

Study Design	Randomised, open, comparative
Study Sites	68 sites, multinational
Study Dates	24 June, 1998 – 26 July 2001
Major Entry Criteria	• metastatic breast cancer • first-line treatment of advanced disease • measurable or evaluable disease • LVEF ≥ lower limit of normal • Normal haematologic, renal and hepatic function • or elevated bilirubin/ ALT/AST up to 4x upper limit of normal if secondary to liver metastases • prior adjuvant anthracycline therapy with a cumulative doxorubicin dosage (or doxorubicin-equivalent) ≤300 mg/m^2 or a cumulative epirubicin dosage ≤540 mg/m^2.
Caelyx Dosing	50 mg/m^2 every 4 weeks
Comparator Dosing	Doxorubicin 60 mg/m^2 as an infusion up to 60 min. every 3 weeks
Duration of Treatment	Until unacceptable toxicity or disease progression
Primary Efficacy Variable (s)	Progression-free survival Cardiac toxicity
Secondary Efficacy Variables	• Overall survival Overall response rate; Clinical benefit response; Health-related quality of life; and Health care resource utilisation
Safety Variables	Adverse events and laboratory tests

This pivotal phase III open label study was conducted in multiple centres across Europe, Canada, South America and Israel. The purpose of the study was to demonstrate that Caelyx was non-inferior to doxorubicin with regard to progression free survival and that Caelyx was superior to conventional doxorubicin with regard to cardiac toxicity.

509 patients with metastatic breast cancer were randomised to receive either Caelyx 50 mg/m^2 every 4 weeks by IV infusion or conventional doxorubicin 60mg/m^2 IV every 3 weeks. The primary endpoints were a comparison of progression free survival and cardiac toxicity. Secondary endpoints included overall survival, and response rate.

Subjects were stratified prior to randomisation according to the following parameters: 1) previous adjuvant anthracycline therapy; 2) presence of bone metastases as only site of disease; and 3) the presence of any one of the following cardiac risk factors: prior mediastinal irradiation, age ≥65, history of heart disease (previous MI, arrhythmia, or angina), hypertension, or diabetes that required medical treatment. Due to characteristic side effects, a double blind design was not considered to be possible.

Cardiac toxicity during treatment and follow-up 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 institution's lower limit for normal). Subjects were also assessed for signs and symptoms of congestive heart failure (CHF).

Tumour response status was evaluated clinically every 3 weeks for doxorubicin and every 4 weeks for Caelyx and by diagnostic scans (CT or MRI, and bone scan) every 3 months. The protocol states: "Radiologic studies of all responding patients (CR, PR) must be made available for subsequent central review". According to the protocol, assessment of tumour status was to continue every 3 months after discontinuation of therapy, until progressive disease had been shown. According to the analysis plan,

subjects with no tumour assessment and who did not die within 4 months after the last assessment were to be censored. Deaths within 4 months of the last assessment were considered events.

Results.
Baseline patient characteristics are shown in tables 2 and 3.

Table 2. Demography data

		Number (%) of Subjects	
		CAELYX (n=254)	Doxorubicin (n=255)
Age (years)			
<50		60 (23.6)	66 (25.8)
50–65		123 (48.4)	129 (50.5)
>65		71 (27.9)	60 (23.5)
Median		59	58
Premenopausal		78 (30.7)	90 (35.2)
Postmenopausal		175 (68.8)	159 (62.3)
Performance Status (WHO)	0	137 (53.9)	125 (49.0)
	1	94 (37.0)	101 (39.6)
	2	23 (9.0)	28 (10.9)

Table 3. Baseline Disease Characteristics

		Number (%) of Subjects	
		CAELYX (n=254)	Doxorubicin (n=255)
Number of Metastatic Sites	1	94 (37.0)	104 (40.7)
	2	83 (32.6)	79 (30.9)
	>2	77 (30.3)	72 (28.2)
Metastatic Site	Visceral	149 (58.6)	143 (56.0)
	Bone Only	24 (9.4)	26 (10.1)
Sites of Metastases[a]	Brain	1 (0.4)	2 (0.8)
	Chest wall	29 (11.4)	27 (10.6)
	Abdomen	5 (2.0)	6 (2.4)
	Bone	125 (49.2)	111 (43.5)
	Lung	90 (35.4)	93 (36.5)
	Lymph Nodes	116 (45.7)	121 (47.5)
	Liver	88 (34.6)	79 (31.0)
	Pleural Effusion	36 (14.2)	33 (12.9)
	Other	43 (16.9)	36 (14.1)
Oestrogen Receptor Status	Negative	54 (21.2)	59 (23.1)
	Positive	90 (35.4)	102 (40.0)
	Unknown	110 (43.3)	94 (36.8)
Prior Oncology Therapy[b]	Yes	166 (65.3)	158 (61.9)
	Adjuvant only	23 (9.0)	20 (7.8)
	Advanced only	128 (50.3)	129 (50.5)
	None Specified	88 (34.6)	97 (38.0)
Disease Free Interval[c]	0-<12	102 (40.1)	101 (39.6)
	12-<24	26 (10.2)	22 (8.6)
	24-<36	38 (14.9)	27 (10.5)
	≥36	88 (34.6)	105 (41.1)
	Median	23.65	25.2
Months from Metastatic Diagnosis to Randomizsation			
	0-<1	108 (42.5)	98 (38.4)
	1-<2	51 (20.0)	54 (21.1)
	≥2	95 (37.4)	103 (40.3)
	Median	1.1	1.3

		Number (%) of Subjects	
		CAELYX (n=254)	Doxorubicin (n=255)
Baseline Cumulative Anthracycline Dose (mg/m^2)			
	None	216 (85.0)	215 (84.3)
	>0-<150	6 (2.3)	5 (1.9)
	150–300	31 (12.2)	33 (12.9)
	>300	1 (0.3)	2 (0.7)
Cardiac Risk Factors	No	132 (51.9)	134 (52.5)
	Yes	122 (48.0)	121 (47.4)
Mediastinal irradiation[d]		11 (4.3)	8 (3.1)
History of heart disease[d]		1 (0.4)	1 (0.4)
History of hypertension[d]		30 (11.8)	42 (16.5)
Age ≥65[d]		37 (14.6)	33 (12.9)
≥2 Risk factors		43 (16.9)	37 (14.5)

a: A subject may have more than 1 metastatic site.
b: Chemotherapy or hormonal therapy.
c: Months from primary diagnosis to metastatic disease.
d: Number of subjects with only this risk factor.

There were 28% of patients in the doxorubicin arm and 43% in the Caelyx arm discontinued due to progressive disease. Reasons for discontinuation are presented in table 4.

Table 4. Primary Reason for Discontinuation

	CAELYX (n=254)	Doxorubicin (n=255)
Disease progression	104 (42.5)	72 (28.2)
1 -<3 months after randomisation	39 (15.4)	32 (12.5)
3-<6	35 (13.8)	34 (13.3)
6-<9	22 (8.7)	6 (2.4)
9+	12 (4.7)	0
Investigator Discretion	60 (23.6)	92 (36.1)
Adverse events	56 (22)	24 (9.4)
Cardiac toxicity	6 (2.4)	36 (14.1)
Subject request	16 (6.3)	25 (9.8)
Noncompliance	2 (0.8)	6 (2.4)

Progression-free survival. The median progression free survival was 6.9 months in the Caelyx arm and 7.8 months in the conventional doxorubicin arm (table 5 and Figure 1).

Table 5. Progression Free Survival for trial I97-328

	Number of Subjects						
	n	Censored	Progressed[a]	Median PFS	p-value[b]	HR	95% CI for HR[c]
Caelyx	254	52	202	6.9 months	0.99	1.00	0.82-1.22
Doxorubicin	255	47	208	7.8 months			

a: Deaths within 4 months of last tumor evaluation indicating no progression also are considered events.
b: Stratified log rank test to test superiority of CAELYX to doxorubicin.
c: Adjusted for the interim analysis (95.01% CI provided).

Figure 1. Progression free survival for trial I97-328

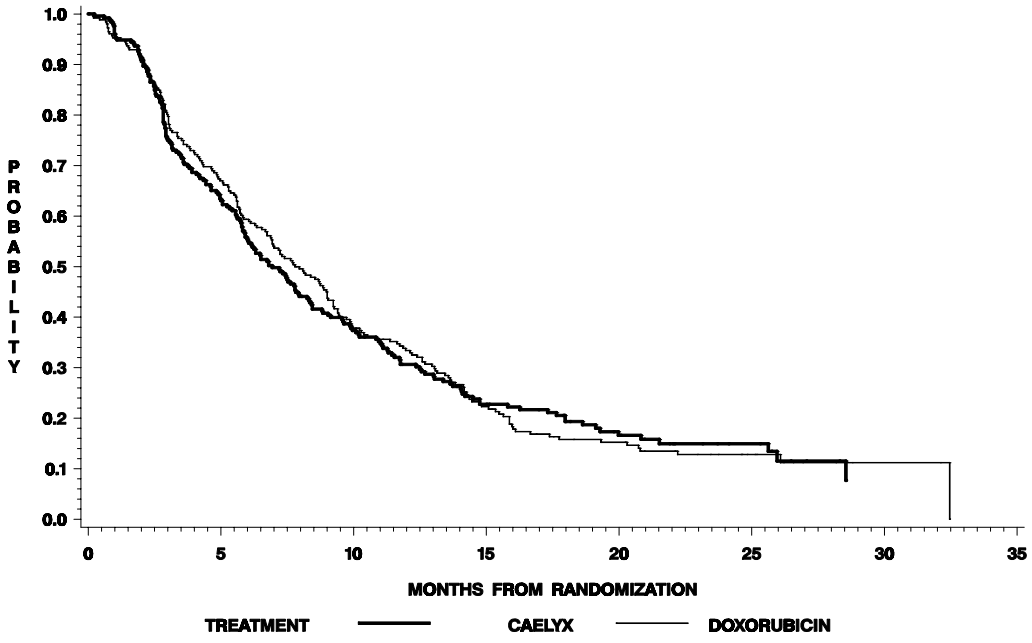

Figure 2. Overall survival for trial I97-328

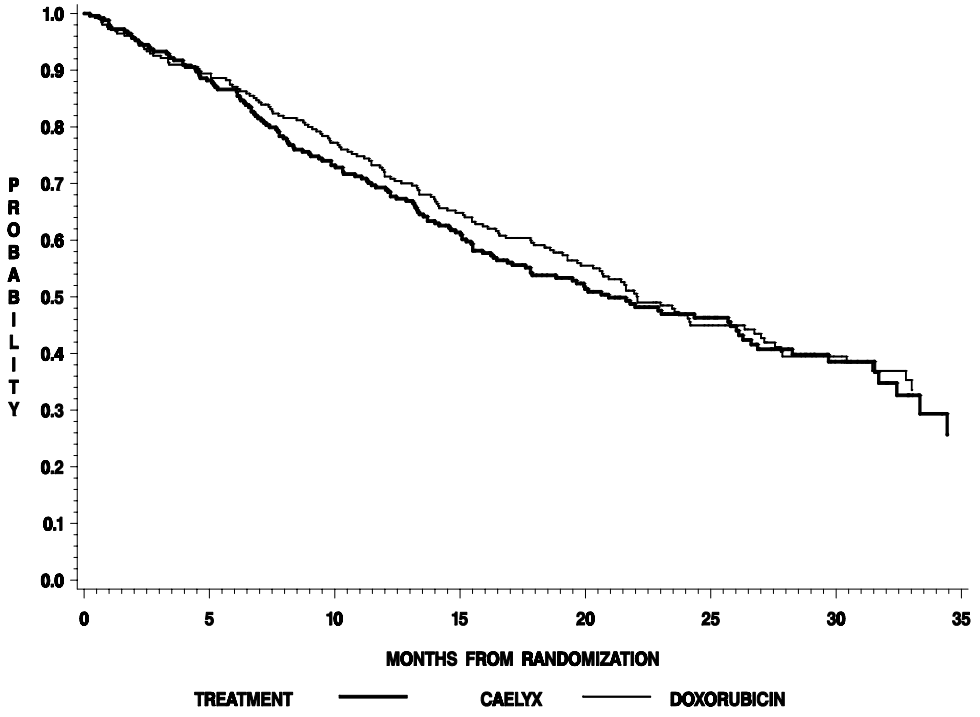

Table 6. Overall survival for trial I97-328

	n	Censored	Dead	Median OS	p-value[a]	HR	95% CI for HR[b]
Caelyx	254	110	144	21 months	0.59	0.94	0.74–1.19
Doxorubicin	255	113	142	22 months			

a: Stratified log rank test to test superiority of CAELYX to doxorubicin.
b: Adjusted for the interim analysis (95.01% CI provided).

Tumour response

There were altogether 410 patients with measurable disease, but of these 103 were not evaluated for tumour response. In the majority, these patients received less than 12 weeks of therapy and "an assessment was not required by the protocol" (study report).

Objective Response (WHO) (patients with measurable disease) 33% of patients who received Caelyx were classified as responders (CR & PR) compared to 38% who received conventional doxorubicin.

Table 7. Tumour response results for trial I97-328

	CAELYX (n=209)	Doxorubicin (n=201)	95% CI for difference
Overall Response (CR+PR)	68 (33)	77 (38)	-15%; +4%
CR	7 (3)	9 (4)	
PR	61 (29)	68 (34)	
Stable Disease (SD)	52 (25)	51 (25)	
Progressive Disease (PD)	37 (18)	22 (11)	
No Assessment	52 (25)	51 (25)	

Quality of life assessment was undertaken using the EORTC QLQ-C30 questionnaire. At the 12-week time point specified, the results significantly favoured doxorubicin over Caelyx with 32% and 20% of patients respectively achieving a "Clinical Benefit Response" (CBR). However, mean changes from baseline for all functioning domains throughout cycles 1-4 were small (<8 points) in both groups. EORTC QLC-C30 symptom scores were comparable with both Caelyx and doxorubicin, and palliation of disease-related symptoms was observed in both treatmnent groups.

Cardiac toxicity results are described under "Safety"section.

Study C/I96-352.

Study C/I96-352 was a phase III open label study which employed a randomised open label parallel group design, which was submitted in support of the salvage indication: "treatment of women with metastatic breast cancer who had failed first- or second-line therapy with a taxane-containing regimen" (this claim was withdrawn by the MAH*)*. The trial compared Caelyx with 2 salvage regimens in women with metastatic breast cancer who had failed first-or second-line therapy with a taxane-containing regimen. 301 patients were randomised to receive either Caelyx 50mg/m^2 every 4 weeks or alternatively either vinorelbine 30mg/m^2 weekly or a combination of mitomycin C 10mg/m^2 IV on Days 1 and 28 and vinblastine, 5 mg/m^2 IV on days 1, 14, 28 and 42 for 2 cycles (Days 1-56); subsequent cycles: mitomycin C, 10 mg/m^2 IV on day 1 and vinblastine at 5 mg/m^2 IV on Days 1 and 21. Mitomycin C was administered at 6-8 week intervals after adequante hematologic recovery. The choice of this alternative comparator regimen was at the discretion of the investigator. Of the patients enrolled on the comparator arm, 85% received vinorelbine.

The primary efficacy criterion was progression free survival. Secondary efficacy variables included overall response rate, response duration and overall survival. The primary objective of the study was originally to show the superiority of Caelyx to the active comparator, with regard to Progression Free Survival. However, when this superiority was not demonstrated, the results were reconsidered in terms of non-inferiority of Caelyx to the active comparator regimens.

Progression-free survival, showed a trend in favour of treatment with Caelyx which did not achieve significance [Hazard Ratio = 1.26 ; (95% CI 0.98-1.62)].

Overall Survival showed no significant difference between the treatments

[Hazard Ratio = 1.07 ; (95% CI 0.79-1.45)]

Objective Response Rate was similar between the treatments at around 10%.

Quality of life assessment was undertaken using the EORTC QLQ-C30 questionnaire. At the 12-week primary time point, 10% of Caelyx patients achieved a "Clinical Benefit Response" (CBR) compared with 7.9% of comparator patients.

Cardiac toxicity was defined as a decrease of 15% or greater from Baseline or a 5% or greater decrease from Baseline and the LVEF became abnormal. Results are described under "Safety" section

Safety

Table 8. Sources of Safety Data

Source	No. of Caelyx-Treated Subjects	Type of Data
Caelyx as Monotherapy		
Protocol I97-328	254	Comparative safety data vs. doxorubicin)
Protocol C/I96-352	150	Comparative safety data vs. Vinorelbine or mitomycin c + vinblastine
Integrated safety results of 16 clinical trials of Caelyx as a single agent a variety of solid tumours	929	Adverse events and clinical laboratory data
Experience with Caelyx Used in Combination With Other Chemotherapeutic Agents		
Integrated safety results of 8 clinical trials of CAELYX in combination with other chemotherapeutic agents against a variety of solid tumours	222	Adverse events and clinical laboratory data
Additional Information		
Postmarketing experience	65,400	Spontaneous safety reports

- Deaths

The number of deaths within 30 days after treatment completion was altogether 61 in the two pivotal studies, evenly distributed between Caelyx and comparators.

- Serious adverse events

In protocol I97-328, SAEs were reported by 34% of Caelyx and 26% of doxorubicin subjects. The pattern was overall consistent with the general pattern of AEs during the trial. Individual SAEs occurred in 2% or fewer subjects in either group with the exception of dyspnea (4%) and palmar-plantar erythrodysesthesia (PPE) (6%) in the Caelyx group, fever (6%) and nausea (4%) with doxorubicin, vomiting (3% Caelyx, 5% doxorubicin), and neutropenia (3% Caelyx, 7% doxorubicin).

Excluding subjects who died, there were 27 subjects in protocol C/I96-352 who discontinued treatment due to an AE, some of whom also had an AE while on treatment, 15 Caelyx subjects, 11 vinorelbine subjects and 1 mitomycin C + vinblastine subject. Excluding subjects who died and those who discontinued treatment due to AE, there were 58 subjects who experienced a serious AE or a medically significant event while on treatment, 32 Caelyx subjects, 23 vinorelbine subjects and 3 mitomycin C + vinblastine subjects.

The percentage of subjects who discontinued because of adverse events was similar among the breast cancer and solid-tumour studies: 24% in Protocol I97-328; 19% in Protocol C/I96-352; and 16% in the solid-tumour studies.

Table 9. Most Common Adverse Events Cited as a Reason for Discontinuation

	No. (%) of Subjects		
Type of Adverse Event	I97-328(n=254)	C/I96-352 (n=150)	All Solid Tumour (n=929)
PPE /skin toxicity	21 (8)	14 (9)	64 (7)
Infusion reactions	4 (2)	2 (1)	19 (2)
Stomatitis/mucositis	5 (2)	0	22 (2)
Cardiac	2 (<1)	1 (<1)	13 (1)
Hematologic	4 (2)	3 (2)	26 (3)

Table 10. Most Frequently Reported (— to 1%) Treatment-Related Grade 3 or 4 Adverse Events in Randomised Breast Cancer Studies

	Protocol No. I97-328 (n=254)		Protocol Nos. C/I96-352 (n=150)	
	Grade 3	Grade 4	Grade 3	Grade 4
No. (%) of Subjects Reporting Treatment-Related Adverse Events[a]	**101 (40)**	**10 (4)**	**57 (38)**	**6 (4)**
Hand-foot syndrome/PPE	42 (17)	0	27 (18)	1 (<1)
Stomatitis	12 (5)	0	7 (5)	0
Mucositis nos	10 (4)	0	4 (3)	0
Asthenia	3 (1)	0	2 (1)	0
Fatigue	2 (<1)	0	6 (4)	0
Vomiting	2 (<1)	0	6 (4)	0
Nausea	8 (3)	0	5 (3)	0
Rash	6 (2)	0	2 (1)	1 (<1)
Abdominal pain	3 (1)	0	1 (<1)	0
Dyspnea	2 (<1)	1 (<1)	3 (2)	1 (<1)
Diarrhea	3 (1)	0	1 (<1)	0
Fever	0	0	1 (<1)	0
Pain	1 (<1)	0	2 (1)	0
Allergic reaction	3 (1)	1 (<1)	0	0
Alopecia	0	0	0	0
Erythema	2 (<1)	0	3 (2)	0
Headache	1 (<1)	0	2 (1)	0
Anorexia	3 (1)	0	0	0
Musculoskeletal pain	4 (2)	0	1 (<1)	0
Dermatitis exfoliative	3 (1)	0	0	0
Rash Maculopapular	3 (1)	0	0	0

Potential Treatment-Limiting Toxicities

Four toxicities have been shown to be potentially treatment-limiting for CAELYX monotherapy:

- Cardiac Toxicity
- Palmar-Plantar Erythrodysesthesia.
- Stomatitis,
- Infusion Reactions, which are not related to dose but can cause an interruption of a dose and, in severe cases, lead to discontinuation.

Cardiac Toxicity (co-primary endpoint in study I97-328)

Results of cardiotoxicity assessment as defined by LVEF and CHF signs and symptoms assessment are presented in Table 11. Overall, 339 subjects had electronic multigated radionucleotide (MUGA) scan data available for cardiotoxicity evaluations by the investigators (baseline and at least one scan during treatment). (Note: MUGAs were not required for subjects with low cumulative anthracycline doses.)

Table 11. Patients meeting cardiac toxicity criteria during treatment and follow-up for trial I97-328

	Caelyx (n=254)	Doxorubicin (n=255)	95% CI for difference
Cardiotoxicity (LVEF defined)	10	48	-20% to –9.4%
With signs or symptoms of CHF	0	10	
No signs or symptoms of CHF	10	38	

Additionally, 2 Caelyx subjects and 2 doxorubicin subjects, who did not have cardiotoxicity by LVEF criteria, developed signs and symptoms of heart failure during or after study treatment. Of note, one of the Caelyx subjects developed heart failure after only 1 cycle and the other after 2 cycles.

Of the 230 subjects who had electronic MUGA data available for independent review, 3 Caelyx subjects and 30 doxorubicin subjects met the protocol-specified LVEF criteria for cardiotoxicity.

Table 12. Cumulative Anthracycline Dose at First Cardiac Event

	Caelyx (n=254)				Doxorubicin (n=255)			
Cumulative Dose (mg/m^2)	Censored	Cardiac Event	Continued.	Cum. % Cardiac Event[a]	Censored	Cardiac Event	Continued.	Cum. % Cardiac Event[a]
≤100	41	0	213	0	16	0	239	0
>100-200	51	3	159	2	30	0	209	0
>200-300	49	1	109	2	35	12	162	6
>300-400	37	3	69	6	39	9	114	12
>400-450	23	3	43	11	23	7	84	18
>450-500	7	0	36	11	19	9	56	28
>500-550	10	0	26	11	28	6	22	40
>550-600	9	0	17	11	8	1	13	43
>600	17	0	0	11	9	4	0	83

a: Kaplan-Meier estimate.

Anthracycline administered in the adjuvant situation is included in the cumulative dose estimates. If there is a difference in cardiotoxicity between Caelyx and conventional doxorubicin, this way to handle data is conservative.

In study C/I96-352, a total of 22 subjects met the protocol-specified criteria for discontinuation due to cardiac toxicity, but apparently the majority experienced non-specific declines in LVEF, secondary to co-morbid conditions, such as disease progression. The number of cardiac biopsies is limited, however, but in a prior study, biopsy results of 10 KS subjects with cumulative Caelyx doses from 469 to 860 mg/m^2 showed minimal cardiotoxicity.

Palmar-Plantar Erythrodysesthesia (PPE)

The incidence and severity of PPE was similar among breast cancer subjects and subjects in the solid-tumour studies. The majority of reports of PPE were managed by delaying or reducing the dose.

In the breast cancer studies, the occurrence of PPE in cycle 1 was 7% to 10%. In the breast cancer studies and in the solid tumour studies, the incidence of PPE peaked in Cycles 2 and 3 of Caelyx treatment, and then declined in Cycles 4, 5, and 6

Stomatitis

Approximately 20% of subjects in the breast cancer studies and 36% of solid-tumour subjects experienced treatment-related stomatitis. No breast cancer subject reported Grade 4 stomatitis, and Grade 4 stomatitis was uncommon among subjects in the solid-tumour studies (<1%, 5/929).

Infusion Reactions

Infusion reactions were characterised by the following adverse events: allergic reaction, anaphylactic reaction, face oedema, flushing, hypotension, urticaria and wheezing. Approximately 12% of breast cancer subjects experienced an infusion reaction. One subject in the breast cancer studies, experienced a Grade 4 allergic reaction with the initial dose that was successfully managed with additional therapy and dose interruption, and the subject continued therapy for 13 cycles.

A total of 6 breast cancer subjects discontinued therapy because of an infusion reaction, 4 in Protocol No. I97-328, and 2 in Protocol C/I96-352. In all 4 subjects in Protocol I97-328, the infusion reactions were associated with immediate or delayed-type hypersensitivity.

Of the 2 subjects in Protocol Nos. C/I96-352 who discontinued because of infusion reaction, one had mild flushing and severe wheezing immediately after the first CAELYX dose and the other had severe skin flushing also after the first dose.

A total of 100 solid-tumour subjects (100/929, 11%) experienced an infusion reaction following the first CAELYX dose. These reactions led to discontinuation in 19/929 subjects.

Discussion of efficacy in first line treatment.

The population in study I97-328 appeared representative for patients with advanced breast cancer at the time of first-line chemotherapy. The outcome with respect to PFS appeared very similar between treatment arms and the non-inferiority criterion set out in the protocol that the lower bound of the confidence interval should be above 0.80, was met. Several concerns were identified relating to the design and conduct of the study that it was considered might affect the interpretation of study data.
The study was not powered to compare survival between the two treatments. However, the median overall survival was 21 months for those who received Caelyx and 22 months for those who received conventional doxorubicin (HR 0.94, 95% CI 0.74- 1.19). Although acceptance limits were not defined in the protocol, the 95% CI reflects at worst a possible loss of 26% (HR 0.74) corresponding to a possible loss in median survival of about 6 months (i.e. 22-6 = 16 months) or at best a possible gain of 19% (HR 1.19) corresponding to a gain in median survival of about 4 months (22+4 = 26 months). This range of overall survival (16-26 months) is consistent with that seen for anthracycline-based therapy in first-line treatment of metastatic disease.

The high discontinuation rate prior to disease progression, and the imbalance in the rate of such withdrawals between the two groups was a concern in the assessment of non-inferiority. The imbalance was mainly caused by a higher proportion of withdrawals due to "investigator discretion" in the conventional doxorubicin group. Withdrawal due to "investigator discretion" in the doxorubicin arm "typically represented" (study report) patients approaching a cumulative anthracycline dose of 550 mg/m^2. "Cardiac toxicity" in a wide sense was, thus, a major cause for discontinuation in the doxorubicin arm.

Overall it appeared that in this head-to-head comparison with conventional doxorubicin and on a mg for mg level, the outcome in terms of cardiotoxicity is favourable for Caelyx, with the caveat that the clinical relevance of MUGA scan deterioration may be disputed. The differences between treatment arms in withdrawal rates due to "cardiac toxicity" and other adverse events are prominent.
The following concerns were raised:

- Study I97-328 was designed as a non-inferiority study in terms of progression-free survival compared with conventional doxorubicin. Due to the following concerns, all considered to be of importance in the assessment of non-inferiority results, the study is considered inconclusive.
- The non-inferiority margin has not been justified.
- There was no external, treatment-blinded assessment of time to progression.
- The three-month interval between scheduled imaging is regarded as too long.
- The eligibility of patients administered adjuvant anthracyclines will affect the possibility to optimally administer conventional doxorubicin.
- The study population is considered representative, but also heterogeneous with respect to prognostic factors.
- Only 28% of the doxorubicin and 43% of the Caelyx patients discontinued due to progressive disease
- Data on number of censored patients prior to documented tumour progression should be presented
- In patients withdrawn prior to progression, data on next-line therapy should be provided
- There were more patients in the doxorubicin treatment group than in the Caelyx group who were censored prior to disease progression, which might affect the assessment of non-inferiority.

These points were discussed with the MAH during an oral explanation:

Discussion of efficacy in the treatment of patients who have failed taxane containing regimen
In study C/I96-352, the proportion of responders was considered too small and the duration of Progression Free Survival too short to be of clinical value, bearing in mind the high frequency and severity of PPE and also the frequency of cardiotoxicity. The rationale of including a high proportion of patients whose disease had progressed despite the use of anthracycline containing regimens in study C/I96-352 was questioned since in clinical practice further use of an anthracycline would not be considered in this situation. With regard to this, in relation to cardiac safety, it was not considered that a beneficial effect on cardiac safety has been established for cumulative anthracycline doses in excess

of 450mg/m^2 in this study since 14/150 *Caelyx* treated patients developed cardiotoxicity at cumulative doses less than this figure.
The results of the single study C/I196-352 conducted in heavily pretreated patients which failed to demonstrate the superiority of Caelyx were considered insufficient to support the indication for Caelyx in patients who have failed previous treatments. In conclusion, the risk-benefit assessment for the indication for the patients who have failed a taxane- containing regimen has not been demonstrated. Subsequently the MAH withdrew this proposed indication.

Discussion of Safety

With regard to safety, quality of life was considered to be a primary consideration. In relation to this, it was considered that the relative risk-benefit of *Caelyx* might not be favourable compared to conventional formulations of doxorubicin the proposed first line indication for the following reasons: (i)The observation from the "Quality of Life" data from study I97-328 showed that conventional doxorubicin is superior to Caelyx. (ii) The adverse effects which occurred in association with Caelyx, particularly the high frequency and severity of palmar-plantar erythrodysesthesia (PPE), were considered to be more burdensome for patients' quality of life than the adverse effects which occurred in association with conventional doxorubicin. However, it was conceded that PPE was not life-threatening and was reversible.

These points were extensively discussed with the MAH during the Oral Explanation. It was agreed that clear instructions on the prevention and minimisation of PPE should be included in the SPC and Package Leaflet.

In relation to cardiotoxicity concern was expressed regarding the potential for Caelyx to cause cardiotoxicity at high cumulative doses. Since no data nor scientific literature exist to show enhanced efficacy for Caelyx at high cumulative doses compared to conventional doxorubicin formulations, it was agreed that the proposed SmPC should continue to recommend evaluation of LV function for every Caelyx administration in excess of 450mg/m^2.

It was concluded that Caelyx should be indicated as monotherapy for the first line treatment of metastatic breast cancer in those patients at increased cardiac risk. It was considereed that it presents a more favourable profile in terms of cardiotoxicity as compared to conventional formulations of doxorubicin.

Furthermore, the SPC was amended to clearly specify severity and duration of the main adverse events: alopecia, nausea/vomiting, neutropenia, PPE, mucositis and stomatitis.

By granting the above indication it was considered that physicians can have the option to use either Caelyx or conventional doxorubicin, with their differing adverse event profiles on the basis of individual patient choice.

Benefit/risk assessment

Overall, the efficacy outcome with respect to PFS appeared very similar between Caelyx and conventional doxorubicin and the non-inferiority criterion set out in the study protocol was met, but a number of methodological points did not allow a more definite conclusion to be made. Furthermore, the outcome in terms of cardiotoxicity is clearly favourable for Caelyx.
The CPMP, based on the review of data on safety and efficacy, considered by consensus that the benefit / risk ratio of Caelyx in the indication: *"As monotherapy for patients with metastatic breast cancer, where there is an increased cardiac risk.*" is favourable and therefore recommended the granting of the indication.