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**Background Information  
Regarding Accelerated Approval of  
DOXIL<sup>®</sup> in AIDS-Related Kaposi's  
Sarcoma**

**Phase 4 Commitment**

**DOXIL<sup>®</sup> (doxorubicin HCl liposome injection)  
NDA 50-718**

Oncologic Drugs Advisory Committee (ODAC) Meeting  
8 November 2005  
Bethesda, MD

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# Background Information Regarding Accelerated Approval of DOXIL<sup>®</sup> in AIDS-Related Kaposi's Sarcoma

## PHASE 4 COMMITMENT

### 1. SUMMARY

This document provides an overview for the Oncologic Drugs Advisory Committee (ODAC) members of the role of DOXIL<sup>®</sup> (doxorubicin HCl liposome injection)\* in the treatment of AIDS-related KS and the status of the Phase 4 commitment for this indication. DOXIL<sup>®</sup> (doxorubicin HCl liposome injection) is doxorubicin HCl formulated as a pegylated liposome.

DOXIL<sup>®</sup> (doxorubicin HCl liposome injection)\* received accelerated approval on 17 November 1995 for the treatment of chemotherapy refractory AIDS-related Kaposi's sarcoma (AIDS-related KS). This accelerated approval was originally granted to the 'SEQUUS Corporation' along with the Phase 4 commitment to: "Conduct a randomized clinical study of DOXIL versus DaunoXome". All activities related to the Phase 4 commitment have been conducted in close collaboration with the FDA, during a period when the incidence of and treatment options available for the disease have changed dramatically. This summary, is followed by a more detailed discussion of the clinical development and regulatory history for the product in this indication, including the results and reanalysis of the primary study conducted to satisfy the Phase 4 commitment for full NDA approval. Two additional, more recent publications of investigator-initiated studies are also discussed, which reinforce the clinical utility of DOXIL in AIDS-related KS, but also the difficulties in conducting such studies.

In March 1999, the NDA was transferred to the ALZA Corporation. The ALZA Corporation then became part of Johnson & Johnson in 2001. The original approval was based on objective tumor response from 77 patients retrospectively identified from an interim analysis of 383 refractory patients in an open-label, single-arm, multicenter study.

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\* DOXIL is known as CAELYX in countries outside the US, Israel and Japan and is marketed by the Schering-Plough Corporation in Kenilworth NJ.

The Phase 4 commitment, Study 30-38 entitled, “A Double-Blind, Randomized Evaluation of Clinical Benefits of DOXIL in Patients with AIDS-Related Kaposi’s Sarcoma Treated with DOXIL or DaunoXome<sup>®</sup>” was designed in close collaboration with the FDA, and initiated in September 1996. The study enrolled 80 patients and took 4 years to complete. During the course of this study, the treatment for AIDS changed significantly with the introduction of highly active anti-retroviral therapy (HAART) in late 1996. The primary endpoint was improvement in clinical benefit, defined as a sustained (at least 4 weeks) improvement from baseline in at least one of the five AIDS-related KS symptom categories in the absence of disease progression or severe drug-induced toxicity.

In Study 30-38, 80% (48/60 subjects) of the DOXIL-treated patients and 63.2% (12/19) of the DaunoXome-treated patients experienced clinical benefit, defined as a sustained (at least 4 weeks) improvement from baseline in at least one of the five AIDS-related KS symptom categories in the absence of disease progression or severe drug-induced toxicity.

Using a more conservative definition of clinical benefit, requiring improvement in at least one symptom category that lasted at least 4 weeks, no worsening of other symptom categories and no increase in medical interventions either before or during that period, 36.7% (22/60) DOXIL-treated patients and 15.8% (3/19) of the DaunoXome-treated patients experienced clinical benefit.

Partial tumor responses (objective tumor response was a secondary endpoint) were observed in 55% of DOXIL-treated patients and in 31.6% of those treated with DaunoXome. In all cases there was a positive correlation between tumor response and clinical benefit.

After submission of the Study 30-38 data on 31 July 2002 as a supplemental New Drug Application (sNDA), the FDA communicated to Johnson & Johnson Pharmaceutical Research & Development L.L.C. (J&JPRD) that the introduction of HAART during the conduct of the study made it difficult for the FDA to interpret the clinical benefit of DOXIL.

Although J&JPRD believed that the results of this study showed sufficient clinical benefit to justify full approval of DOXIL in AIDS-related KS, the FDA’s interpretation was that the clinical benefit of DOXIL and DaunoXome was confounded by HAART. The Agency determined that the numbers of DOXIL (n=21) and DaunoXome (n=10) patients not confounded

by changes in antiretroviral therapy prior to initiation of treatment were not sufficient to make a definitive conclusion regarding the clinical benefit of the patients treated with DOXIL, resulting in a non-approvable recommendation for the sNDA.

In the March 2003, the DOXIL application along with other products granted approval under accelerated conditions also with outstanding Phase 4 commitments were reviewed by ODAC. Subsequent to the ODAC review, discussions between J&JPRD, the FDA in June 2004, resulted in an agreement that J&JPRD would conduct a re-analysis of Study 30-38 to evaluate confirmed tumor response among patients who had not experienced changes in their anti-retroviral therapy from 60 days prior to study treatment until first response was observed. The results of this re-analysis showed that the confirmed tumor response was 50% or 55% irrespective of whether we analyzed for only those patients stabilized on anti-retroviral therapy for 2 months, or all patients, respectively. This analysis of the Study 30-38 data was submitted to the FDA on 8 October 2004. The FDA subsequently (29 March 2005) indicated to the sponsor that the interpretation of these results was still confounded by changes in HAART and the sponsor chose to withdraw the sNDA.

In 2004, during the review of the updated sNDA, both the FDA and J&JPRD became aware of a recent investigator-initiated study in Spain of DOXIL plus HAART versus HAART alone. This study was conducted in 28 patients between 2000 and 2003 and was designed to compare the evolution of AIDS-related KS in HIV-positive patients receiving DOXIL and HAART to those receiving HAART alone.

The results were published in August 2004 in the journal *AIDS*.<sup>1</sup> The response rate for the DOXIL plus HAART cohort was 76% (10/13 subjects) and 20% (3/15) for the HAART alone cohort ( $P=0.003$ ). Ten of the 15 patients in the HAART alone-treated group went on to receive DOXIL (a more detailed summary of the results from this study are discussed in Section 3.5, Non-Company Sponsored Studies).

The FDA asked J&JPRD to obtain more detailed data from this study to support possible conversion of the NDA to regular approval status. Despite diligent efforts, J&JPRD has not been able to obtain access to the Spanish study database.

More recently, in an uncontrolled observational study conducted in Germany between 1997 and 2002, AIDS-related KS treatment responses were assessed in 54 HIV-1 infected patients with advanced AIDS-related KS. In 81.5% of subjects, who received simultaneous administration of HAART and DOXIL (20 mg/m<sup>2</sup> given every 2 weeks), complete or partial responses were observed within a median of 8 weeks. We are currently attempting to retrieve these data for submission to the FDA.

J&JPRD have given substantial consideration to the conduct of an additional study that might demonstrate the clinical benefit of DOXIL. Based on the body of data previously submitted (including Study 30-38) and the two recent publications that further support the clinical benefit of DOXIL in patients with AIDS-related KS receiving HAART above and beyond the benefits that may be achieved by HAART alone, J&JPRD believes that the totality of data presented provide substantial evidence for the clinical benefit of DOXIL in AIDS-related KS. In addition, we believe that it would be difficult, if not impossible, to conduct a further randomized clinical study in patients with AIDS-related KS for the following reasons:

- **Published Literature:** The recent Spanish and German studies in addition to over 20 publications regarding the use of DOXIL, support the clinical benefit of the product in patients with AIDS-related KS. The randomized study in Spain of DOXIL plus HAART compared to HAART alone shows the superiority of the combination over HAART alone, when comparing the two randomized arms as well as when analyzing the activity of DOXIL after crossover of patients from the single-arm to the combination. The German study reports consistent results similar in magnitude to the Spanish study.

The recent publication of an algorithm for the treatment of AIDS-related KS<sup>20</sup> illustrates current advice provided for these patients and highlights that the recommendation is to use HAART and a liposomal anthracycline to treat patients who progress while on HAART or who have advanced or life-threatening disease.

We think that the acceptance of this treatment paradigm, and the data on which it is based, underlie the difficulty of conducting another randomized study of HAART versus HAART and DOXIL for the treatment of AIDS-related KS.

In light of this information regarding the consistency of the results reported in Study 30-38, and the Spanish and German studies, we believe it would be inappropriate to conduct for another study where a proportion of patients would be randomized to receive less than the standard of care for their condition.

- **DOXIL is the preferred therapy:** DOXIL is commercially available in multiple countries, approved in over 70 countries for this disease and is regarded as the preferred first-line treatment of AIDS-related KS when systemic chemotherapy is appropriate. It is estimated that over the last 10 years, approximately 7,000 patients with AIDS-related KS in the United States have received treatment with this drug product (doxorubicin HCl liposome injection). The acceptance of DOXIL as the standard of care for patients with progressive AIDS-related KS makes it difficult to design and execute a study in which the patients would agree to be assigned to an alternate treatment.
- **Incidence of AIDS-Related KS:** The widespread use of HAART has resulted in a markedly decreased overall incidence of AIDS-related KS. It will be challenging to achieve enrollment targets with the low incidence of AIDS-related KS in the United States and most developed countries.

**HAART utilization:** Patients who present with AIDS-related KS are treated with HAART and DOXIL concomitantly when there is a need to achieve rapid cytoreduction, because of the presenting AIDS-related KS lesions that are life-threatening, symptomatic or cosmetically disfiguring. Regression of AIDS-related KS may take 3-9 months after the initiation of HAART alone as a consequence of viral suppression and immune reconstitution, but with DOXIL the median time to response is 30 days (range 14-82) in Study 30-38.<sup>19</sup>

Protocols that require patients to have documented sustained suppression of viral replication for a long pre-specified period (6-18 months) prior to enrollment into a study evaluating the safety and efficacy of new AIDS-related KS agents in order to differentiate between the activity of HAART and the activity of DOXIL, will result in a significant reduction in the numbers of eligible AIDS-related KS patients.

- **Confounding Impact of HAART Therapy on Interpretation of Data:** As discussed earlier, the changes in antiretroviral therapy that occurred

immediately prior to or during the conduct of Study 30-38 were felt by FDA to confound their ability to adequately assess the effect of DOXIL on AIDS-related KS. As the widespread clinical acceptance and use of HAART did not begin until after Study 30-38 had initiated, the impact of HAART on subjects enrolled in 30-38 was not taken into account when designing the original study.

This issue however still exists in that many patients with AIDS-related Kaposi's sarcoma who require systemic chemotherapy also may require modification of HAART for reasons of efficacy or safety, further complicating their eligibility for a pivotal study or their continued participation in that study. When patients fail one combination, they will receive additional drugs, or a new combination, novel or new investigational anti-retroviral agents, all of which will be concurrent with DOXIL administration. These treatments may confound the interpretation of clinical benefit of DOXIL in any study of patients with AIDS-related Kaposi's sarcoma such that the challenges faced by FDA in their review of Study 30-38 will likely be repeated.

- **Ethical considerations:** Delay of an active therapy of AIDS-related KS is not an acceptable option to either patients or treating physicians. Furthermore, as DOXIL is regarded as the preferred first-line therapy for patients with AIDS-related KS for whom systemic chemotherapy is medically indicated, including in patients receiving HAART, it may be equally as difficult to conduct a study utilizing a "second choice" agent as a comparator. Therefore, we do not believe it is appropriate to conduct such a study.

J&JPRD believes that we have shown due diligence in attempting to address our Phase 4 commitment for DOXIL in AIDS-related KS. We respectfully believe that the overall consistent body of evidence allied to the difficulties described in conducting another randomized study, justify regular approval of the product. We remain eager to work with the Agency to ensure the product remains accessible to this small but highly important patient population.

## 2. GENERAL INFORMATION

**Drug Name:** DOXIL<sup>®</sup> (doxorubicin HCl liposome injection)

**Indication:** DOXIL is indicated for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy.

This indication is based on objective tumor response rates. No results are available from controlled studies that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival

**Accelerated Approval Date:** 17 November 1995

**Indication:** DOXIL is indicated for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy

**Accelerated Approval Date:** 28 June 1999

An sNDA was submitted on 29 March 2004 to convert the accelerated approval to regular approval for the ovarian cancer indication. The sNDA was based on a randomized Phase 3 study of DOXIL compared to topotecan in patients who relapsed or were refractory to prior platinum-based chemotherapy. The results from this study were positive and the FDA approved the sNDA.

**Regular Approval Date:** 29 January 2005

## 3. INTRODUCTION

### 3.1. Overview of AIDS-related Kaposi's Sarcoma

Kaposi's sarcoma (KS) is an acquired immunodeficiency syndrome (AIDS)-defining illness and despite its declining incidence since the introduction of highly active antiretroviral therapy (HAART), AIDS-related KS remains one of the most common neoplasms reported in patients with AIDS. It is associated with significant morbidity and mortality, especially in patients with systemic disease.<sup>2</sup>

AIDS-related KS produces a wide spectrum of clinical manifestations, ranging from asymptomatic cutaneous papules to extensive skin disease with ulcerative plaques and associated edema. Extracutaneous spread of AIDS-related KS is common, especially in the oral cavity, most commonly

affecting the palate and gingival areas that are easily traumatized during mastication, with subsequent pain, ulceration, bleeding and secondary infection. Nutrition and speech may be affected, affecting the patient's overall quality of life. Gastrointestinal involvement has been noted in approximately 40% of patients at initial diagnosis of AIDS-related KS and in up to 80% of patients with AIDS at autopsy. AIDS-related KS gastrointestinal lesions may be associated with weight loss, abdominal pain, nausea and vomiting, gastrointestinal bleeding, and diarrhea. Pulmonary involvement is also common, and may present with shortness of breath, fever, cough, hemoptysis, or chest pain, or it may be an asymptomatic finding on a chest X-ray. AIDS-related KS visceral lesions may be present in patients who have no cutaneous manifestations. Palliation of symptoms is a major goal of AIDS-related KS treatment.<sup>3</sup>

The incidence of AIDS-related KS in the United States has declined since its peak of 4.8 cases per 100,000 in 1989. In the most recent SEER data from 2002 the incidence is 0.7 cases per 100,000.<sup>4,5</sup> This decline was evident before the introduction of HAART. Nonetheless, new cases of AIDS-related KS continue to present, even among patients with viral load suppression resulting from treatment with antiretroviral therapy.<sup>6,7</sup> Despite the low incidence of AIDS-related KS, considerable morbidity and mortality still exist in patients with AIDS who develop AIDS-related KS as a result of failing HAART therapy.

Management and treatment options for AIDS-related KS depend on the extent of the disease, the rate of progression, the presence and severity of symptoms affecting daily activities and quality of life, and the presence of opportunistic infections. The choice of treatment may also be influenced by the severity of the underlying HIV infection, immune system status and by the presence of other co-morbid complications.<sup>3</sup> Some patients with AIDS-related KS have experienced lesion regression after initiation of triple-drug antiretroviral therapy. Optimal antiretroviral therapy may inhibit development or progression of AIDS-related KS in several ways, including treatment of the underlying immunosuppression.

AIDS-related KS treatment can be broadly classified into local or systemic therapy. Local therapy directed at control of individual lesions is appropriate for limited, slowly progressive disease without life-threatening organ involvement. Local approaches are most appropriate for individuals with few and small lesions. Individuals with oral lesions or limited cutaneous disease

(e.g. 25 or fewer small skin lesions that are cosmetically disturbing to the patient) may benefit from local therapy. Treatment modalities include surgical excision of the lesions, cryotherapy, photodynamic therapy, intralesional injections, laser therapy, local radiation therapy, and topical application of various drugs such as topical retinoids. Local treatment does not result in a cure. The goals are to improve the patient's appearance and reduce the suffering and social isolation that AIDS-related KS may cause.<sup>3,8,9,10</sup>

Systemic chemotherapy is medically indicated for individuals with advanced or rapidly progressive AIDS-related KS that causes functional impairment.<sup>10</sup> This group includes patients with extensive or symptomatic cutaneous disease, extensive oral disease, symptomatic tumor-associated edema, or compromised visceral function by pulmonary or gastrointestinal AIDS-related KS. The goals of systemic chemotherapy are to induce durable regression of widespread, disfiguring, or disabling lesions, control or reverse life-threatening visceral disease, reduce functional impairment caused by edema or mucocutaneous disease, and to achieve these benefits with agents that have an acceptable side effect profile. Studies conducted during the pre-HAART era have shown that response rates for single agent chemotherapy including doxorubicin (the active ingredient in DOXIL), bleomycin and vincristine varied widely between 10% to 48%, while the response rates for the combination of active agents have tended to be higher, with ranges of 56% to 88%.<sup>10</sup>

Three cytotoxic drugs have been approved by the FDA for the treatment of HIV-associated KS. DOXIL received accelerated approval on 17 November 1995 based on the results of an interim analysis of a phase 2 open-label, single-arm, multicenter study (n=77). DaunoXome (daunorubicin liposomal) received full approval on 8 April 1996 based on the results of a multicenter open-label, randomized, controlled clinical study (n=227). Taxol (paclitaxel) received full approval on 04 August 1997 based on two phase 2 open-label, single-arm, non-randomized studies (n=85). Although a wide variety of single and combination drug regimens are available for treatment of AIDS-related KS, treatment with one of the FDA-approved liposomal anthracyclines is the current standard of care for first-line therapy for advanced AIDS-related KS.<sup>3,8,9</sup>

Before the approval of DOXIL for this patient population, combination cytotoxic chemotherapy with bleomycin and vincristine (BV) or doxorubicin

(Adriamycin<sup>®</sup>), bleomycin and vincristine (ABV) was considered to be the most effective chemotherapy for AIDS-related KS, with reported response rates of 60 to 80%, but with appreciable toxicity. The initial clinical studies of ABV in AIDS-related KS generally administered doxorubicin at doses of either 40 mg/m<sup>2</sup> every 4 weeks or 20 mg/m<sup>2</sup> every 2 to 3 weeks, with reports of impressive response rates of 84% and 88%, respectively. However, therapy was frequently limited by neutropenia and concomitant non-KS opportunistic infections. In addition to dose-limiting myelosuppression, administration of effective therapeutic doses for extended periods of time was often limited by cardiac, pulmonary, and neurologic toxicities.<sup>3,8,9</sup> While many patients benefited from such agents and regimens, it was not infrequent for patients to die with severe, progressive AIDS-related KS despite of optimal therapy.

DOXIL, a pegylated liposomal formulation of doxorubicin, was developed to extend the short *in vivo* half-life of standard doxorubicin and has been investigated extensively in patients with AIDS-related KS (see Table 1). The pegylated liposomes contain segments of polyethylene glycol attached to the surface, thus delaying uptake by the monocyte macrophage system and increasing plasma residence time. The AUC achieved with DOXIL is 2-3 orders of magnitude larger than the AUC for a similar dose of conventional doxorubicin. In contrast to the triphasic pattern of clearance of conventional doxorubicin (approximate mean half-lives of 12 minutes, 3.3 hours, and 30-40 hours), the biphasic disposition of DOXIL has a short first phase (approximately 5 hours) and a prolonged second phase (approximately 55 hours).<sup>11</sup> The prolonged plasma residence time may allow for greater exposure of the tumor to drug. In a study conducted to assess pharmacokinetics and tissue distribution of DOXIL after intravenous administration, biopsies of AIDS-related KS lesions and adjacent normal skin were obtained from 11 patients at 48 and 96 hours following infusion of DOXIL at a dose of 20 mg/m<sup>2</sup>. The doxorubicin concentration was 3- to 53-times (median 19) higher in the AIDS-related KS lesions than in normal skin at 48 hours after the infusion.<sup>12</sup>

In a randomized comparison of DOXIL monotherapy (20mg/m<sup>2</sup> every 2-3 weeks) with a combination of BV (every 3 weeks) or ABV (every 2 weeks), the DOXIL monotherapy arm was associated with a significantly higher response rate and was less neurotoxic than the combination therapy arm.<sup>3,10</sup>

DOXIL is generally well tolerated with myelosuppression as the most common dose-limiting adverse event in patients with AIDS-related KS. While neutropenia occurs most often, anemia and thrombocytopenia occur less frequently, as do nausea, vomiting and stomatitis. Hand-foot syndrome may occur in some patients, most commonly after 6 to 8 weeks of chemotherapy. Although symptoms may occasionally be severe, adverse events rarely necessitate discontinuation of therapy. Single agent DOXIL has largely replaced combination regimens (ABV and BV) as the first-line systemic treatment because of its safety profile and concomitant improvement in quality of life. In the period between July 2004 and July 2005, approximately 1,240 patients were treated with chemotherapy for AIDS-related KS, of these approximately 68% were treated with DOXIL.<sup>13</sup>

DaunoXome is a liposomal formulation of daunorubicin that has also demonstrated activity in AIDS-related KS and was approved in 1996. In the pivotal study, DaunoXome treatment resulted in an objective response rate that was similar to the control ABV arm (25% vs. 28%).<sup>14</sup> Paclitaxel was approved in 1997 for the treatment of chemotherapy refractory AIDS-related KS. The side effect profile of paclitaxel is well known and includes significant myelosuppression and alopecia. Prolonged paclitaxel therapy may also cause peripheral neuropathy.

The advent of highly active antiretroviral therapy (HAART), led to a dramatic reduction in the incidence of Kaposi's sarcoma (KS) among subjects with acquired immunodeficiency syndrome (AIDS).<sup>1,10,16</sup> In the Multicenter AIDS Cohort Study (MACS) of MSM (i.e., men who have sex with men), rates of KS fell by 66% between 1989-1994 and 1996-1997, coinciding with the period during which HAART use increased substantially.<sup>17</sup> In the Swiss HIV Cohort Study, Ledergerber and colleagues<sup>18</sup> demonstrated a substantial reduction in the incidence of KS, with a relative risk of 0.08 when comparing data from 1992-1994 with that from July 1997-June 1998.

Even with the decreased incidence of AIDS-related KS, AIDS-related KS remains one of the most common neoplasms reported in patients with AIDS. New cases of AIDS-related KS continue to be diagnosed, even among patients with HIV viral load suppression, and AIDS-related KS remains a cause of considerable morbidity and mortality in HIV-infected individuals. Treatment remains palliative, with treatment decisions determined on a case-by-case basis, balancing anti-tumor efficacy and toxicity with quality of life

considerations. For patients with rapidly progressing and disseminated AIDS-related KS, especially those with symptomatic visceral disease, the rapid tumor reduction achieved with systemic chemotherapy, such as DOXIL, even in the face of a stable regimen of HAART, may be a lifesaving intervention.

### **3.2. History of DOXIL Clinical Development in AIDS-related KS**

On 17 November 1995, DOXIL was granted accelerated approval under the accelerated approval regulations 21 CFR 314.500, Subpart H for the treatment of AIDS-related KS in patients with disease that has progressed on prior combination chemotherapy or in patients who are intolerant to such therapy based on the results of an interim analysis from an open-label, single-arm, multicenter study.

On 28 June 1995, in accordance with the accelerated approval regulations, a commitment letter was submitted to the FDA to conduct a double-blind, randomized, confirmatory study to evaluate the clinical benefit of DOXIL in patients with AIDS-KS. The confirmatory study (Study 30-38, *A Double-Blind, Randomized Evaluation of Clinical Benefits of DOXIL in Patients with AIDS-Related Kaposi's Sarcoma Treated with DOXIL or DaunoXome<sup>®</sup>*) was designed in close collaboration with the FDA (13 June 1995 meeting with FDA) and was intended to satisfy the requirements for full approval of DOXIL under Subpart H. The start of this study was contingent upon the approval of DaunoXome (April 1996).

On 02 October 2001, the final clinical study report for Study 30-38 was submitted to FDA as part of an efficacy supplement to NDA 50-718. On 31 July 2002, the FDA communicated to the Sponsor that the results of the clinical study did not provide substantial evidence of a clinical benefit for DOXIL in the treatment of AIDS-related KS. FDA also communicated that antiretroviral therapy may be more effective treatment for AIDS-related KS than any of the available anti-KS agents. Study enrollment occurred from September 1996 to September 2000, coinciding with the introduction of highly active antiretroviral therapy (HAART). Changes in anti-HIV medications during or immediately preceding the clinical study could have had an effect on the AIDS-related KS, making assessment of the effect of DOXIL or DaunoXome on AIDS-related KS difficult. The FDA requested that the Sponsor submit a new clinical study protocol to further assess the clinical benefit of DOXIL in AIDS-related KS, and to satisfy full approval of

the AIDS-related KS indication for DOXIL under the accelerated approval regulations in 21 CFR 314, Subpart H. On 27 November 2002, the Sponsor provided a proposed development plan, protocol outline, and timelines to meet the Phase 4 commitment. A meeting with the FDA on 3 February 2003 discussed a proposed study design. Consensus on an acceptable design was not reached.

Based upon the known clinical activity of DOXIL in this patient population, difficulties in designing an acceptable study, the decreasing incidence of AIDS-related KS in the US, the lack of investigator interest and the fact that DOXIL is considered the drug of choice in this patient population, the Sponsor requested in February 2004, that the Division waive the Phase 4 commitment for DOXIL in the treatment of patients with AIDS-related KS. The Division did not agree but provided an option to appeal to the Office Director.

On 23 June 2004, a meeting with the Division and Office Director was held to discuss this Phase 4 commitment. At the meeting, it was agreed that a re-analysis of Study 30-38 evaluating response rate among patients whose response assessment was not confounded by changes in antiretroviral therapy might support regular approval. A supplemental NDA (sNDA) was submitted 8 October 2004 based on a re-analysis of Study 30-38. The FDA indicated that interpretation of the clinical benefit of DOXIL was still confounded by concomitant HAART administration. We withdrew the sNDA in April 2005 awaiting exploration of the availability of the Spanish data.

In December 2004, the Division requested the data from the Spanish study published in the peer-reviewed journal *AIDS*, of DOXIL plus HAART versus HAART alone and indicated that these data are pertinent to the review of the sNDA. Although we have attempted to do so, we have not been able to provide these data to the FDA. Three of the institutions where the study was conducted were unwilling to participate, because a number of the patients are dead or lost to follow-up. The group was unwilling to provide any data without the full support of all participating institutions.

Eleven studies were conducted by the sponsor that evaluated the use of DOXIL in patients with AIDS-related KS. These studies included two open-label efficacy and safety studies (30-03, 30-12), three randomized comparative studies (30-10, 30-11, 30-38), one study in which cardiac biopsies were obtained (30-21), and 3 studies of long-term treatment with

DOXIL (30-24, 30-25, 30-26). Additional safety data were obtained also from two pharmacokinetic studies (30-05, 30-14). Two additional investigator-initiated studies that address concurrent HAART treatment are discussed.

In the above studies the majority of the patients were male, with patient ages ranging from 21-77 years (median + 38 years).

**Table 1** lists the DOXIL AIDS-related KS studies that have been completed.

**Table 1: DOXIL/Caelyx Clinical Studies in AIDS-Related KS Patients**

Study No.	Design	Treatment, DOXIL Dose (mg/m <sup>2</sup> ); Frequency	No. of pts.	Study Endpoints
30-38	Double-blind randomized evaluation of DOXIL/Caelyx vs. DaunoXome® in patients whose AIDS-related KS progressed on prior systemic combination chemotherapy	20 every 2 weeks for 6 cycles vs. DaunoXome® 40 every 2 weeks for 6 cycles	79	Clinical benefit, objective tumor response, and safety
30-03	Phase 2/3, open, noncomparative; dose escalation and efficacy; multicenter	10, 20, 30, or 40; every 2 weeks	250	Objective response, QOL, safety, plasma and tissue drug levels
30-05	Phase 1, randomized, single dose, crossover in PK comparison with CD	10, 20, or 40; single dose	18	PK, comparison of PK variables, objective response, tissue drug levels, safety
30-10	Phase 3, randomized, parallel, multicenter; comparison to ABV	20; every 2 weeks for up to 6 cycles	258	Compare objective response and safety
30-11	Phase 3, randomized, parallel, multicenter; comparison to BV	20; every 3 weeks for up to 6 cycles	241	Compare objective response and safety
30-12	Phase 3, open, noncomparative, multicenter; efficacy in pts who failed prior therapy, long-term safety and efficacy	20; every 3 weeks (or 2 weeks)	871	Tolerability and efficacy (objective response) of long-term DOXIL treatment
30-14	Phase 1, randomized, crossover DOXIL/Caelyx dose comparison; PK and tissue distribution	10 and 20; every 3 weeks for 1-2 doses	43	PK variables, efficacy (objective response), and of 2 dose levels of DOXIL
30-21	Phase 1/2, open, blinded reading of cardiac biopsy data; retrospective comparison to CD	cumulative, >400; every 3 weeks until cumulative dose reached	10	Cardiac biopsy scores compared for DOXIL- and (historical) doxorubicin-treated patients
30-24	Phase 3, long-term, multicenter (Europe); continuation for patients in other studies or patients having failed combination chemotherapy	20; every 3 weeks for up to 30 cycles	94	Tolerability of long-term DOXIL treatment
30-25	Phase 3, long-term, multicenter (US); continuation for patients in other studies or patients having failed combination chemotherapy	20; every 3 weeks for up to 30 cycles	635	Tolerability of long-term DOXIL treatment
30-26	Phase 3, long-term multicenter (Europe); compassionate use by patients for whom no other therapy is available	20; every 3 weeks for up to 30 cycles	67	Tolerability of long-term DOXIL treatment

NOTES: ABV= Adriamycin® (conventional doxorubicin), bleomycin, and vincristine; BV= bleomycin and vincristine; DaunoXome®=daunorubicin citrate liposome injection; CD=conventional doxorubicin

<sup>a</sup>Enrollment for patients who received at least 1 dose of study drug. Numbers include patients rolled over from some studies into larger follow-up studies.

### 3.3. Phase 4 Commitment Study

#### Study 30-38

Study 30-38 was a Phase 4 prospective, randomized, double-blind, multicenter study of DOXIL and DaunoXome for the treatment of patients with AIDS-related KS. This post-marketing commitment study was designed in collaboration with the Division of Oncology Drug Products and the Office Director. The study was conducted in the US between September 1996 and September 2000, was designed to satisfy the requirements of an Accelerated Approval. The study was not designed to demonstrate the superiority of DOXIL over DaunoXome. Enrollment was limited to patients with AIDS-related KS-associated symptoms that could be evaluated for clinical benefit. After two baseline visits to measure disease, 80 patients with AIDS-related KS of a severity requiring systemic chemotherapy were randomized in a 3:1 fashion to treatment with either DOXIL (20 mg/m<sup>2</sup> every 2 weeks) or DaunoXome (40 mg/m<sup>2</sup> every 2 weeks) for up to 6 cycles (detailed study design parameters are included in **Attachment 1**). At each study visit, patients were evaluated for clinical benefit (defined as an improvement in functional activity, pulmonary or gastrointestinal symptoms, AIDS-related KS-associated pain, self image and tumor response).

The presence of at least one or more of the following AIDS-related KS-associated manifestation was a prerequisite for eligibility for this study: AIDS-related KS-associated edema that impaired the patient's functional activity of the extremities, groin, or face; bronchoscopy-proven symptomatic and evaluable pulmonary KS documented within 3 months prior to study entry, provided that an imaging technique (such as CT scan) could be used for assessment of response and that was not associated with any other manifestation of HIV disease; symptomatic and evaluable gastrointestinal KS documented by endoscopy within 3 months prior to study entry, with symptoms definitely associated with AIDS-related KS and not another manifestation of HIV disease; KS-associated pain reported by the patient to be of moderate severity at a minimum, despite use of analgesics; KS lesions that were disfiguring and impaired the patient's self image or daily activities; 5 or more measurable mucocutaneous lesions.

Patients in the DOXIL-treated group were predominately male (97%), the median age was 38 years (range 23 to 75 years). Using ACTG staging criteria, 57% of patients had poor prognosis for tumor burden, 73% were poor prognosis for immune system, and 58% were poor prognosis for systemic illness at baseline. Median CD4 count was 131 cells/mm<sup>3</sup>. Fifty-

five percent of patients treated with DOXIL had received no prior therapy for AIDS-related KS and only 9% of patients had been treated previously with systemic chemotherapy.

At baseline and throughout the course of the study, patients were asked to assess their status using a validated eleven item symptom questionnaire that involved five symptom categories: lymphedema, pulmonary disease, gastrointestinal disease, disfiguring lesions, and KS-associated pain. Patients were asked to rate the degree to which symptoms interfered with their daily activities, using a four point scale from “symptom absent” to “symptom present and interfered very much with daily activities.”

Forty-eight (80.0%) of the 60 DOXIL-treated patients and 12 (63.2%) of the 19 DaunoXome-treated patients experienced clinical benefit, defined as a sustained (at least 4 weeks) improvement from baseline in at least one of the five AIDS-related KS symptom categories in the absence of disease progression or severe drug-induced toxicity. At least one patient reported clinical benefit in each of the symptom categories.

With a more conservative definition of clinical benefit, requiring improvement in at least one symptom category that lasted at least 4 weeks, no worsening of other symptom categories and no increase in medical interventions either before or during that period, 22 (36.7%) DOXIL-treated patients and 3 (15.8%) DaunoXome-treated patients experienced clinical benefit.

Tumor response was a secondary endpoint. Partial response was defined as no new lesions, sites of disease, or worsening edema; flattening of  $\geq 50\%$  of previously raised lesions or area of indicator lesions decreasing by  $\geq 50\%$ , and response lasting at least 28 days. Tumor responses (all partial responses) were observed in 55% of DOXIL-treated patients and in 31.6% of those treated with DaunoXome. In all cases there was a positive correlation between tumor response and clinical benefit, regardless of which of the two definitions of benefit were applied.

Both study drugs were well tolerated. Nausea, neutropenia, and asthenia were the most common treatment-related adverse events reported for both drugs.

Although J&JPRD believed that the results of this study showed sufficient clinical benefit to justify regular approval of DOXIL in AIDS-related KS,

the FDA's interpretation was that the clinical benefit of DOXIL and DaunoXome was confounded by changes in anti-retroviral therapy, and the Agency determined that the number of DOXIL (n=21) and DaunoXome (n=10) patients not confounded by changes in antiretroviral therapy prior to initiation of treatment were insufficient for the FDA to make a definitive conclusion regarding the clinical benefit of the patients treated with DOXIL, resulting in a non-approvable recommendation for the sNDA.

Subsequent to the March 2003 ODAC Meeting that reviewed the DOXIL application along with other accelerated approval products with outstanding Phase 4 commitments, discussions between J&JPRD, the Division and Dr. Temple in June 2004, resulted in an agreement for J&JPRD to conduct a re-analysis of Study 30-38 to evaluate confirmed tumor response among patients who had not experienced changes in their anti-retroviral therapy from 60 days prior to study treatment until first response was observed.

In the sponsor's re-analysis, which was completed and submitted to the FDA in August of 2004, we used a definition of confounding that was included in correspondence from the FDA to the company in 2002. The results presented in **Table 2** show the responses not confounded, using the FDA definition, were 50% (11/22) for DOXIL-treated patients and 50% for DaunoXome-treated patients (5/10).

	DOXIL <sup>®</sup>	DaunoXome <sup>®</sup>
Not confounded patients	50% (11/22)	50% (5/10)
All patients	55% (33/60)	32% (6/19)

### 3.4. Other Company-Sponsored Studies

#### Study 30-03

Study 30-03, a Phase 2/3 study of pegylated liposomal doxorubicin for the treatment of AIDS-related KS, was initiated in October 1991 and conducted by 23 investigators in seven countries ex-U.S. (Australia, England, Germany, Italy, Portugal, Switzerland, and the Netherlands). The objectives of this study were to determine the incidence of objective response of cutaneous AIDS-related KS to treatment with DOXIL, to evaluate the patients' quality of life during DOXIL therapy, to determine the incidence of acute and chronic toxicity in DOXIL-treated patients, and to determine doxorubicin levels in AIDS-related KS lesions, normal skin, and serum following treatment with DOXIL.

A total of 247 patients with AIDS-related KS (and 1 non-AIDS-related KS patient) were treated with DOXIL in cumulative doses ranging from 10-520 mg/m<sup>2</sup> in this open-label, multicenter, dose escalation study. DOXIL was to be administered every 2 weeks, initially at a dose of 10 mg/m<sup>2</sup>, and if no response was noted after the first two cycles, the dose was doubled for two additional cycles, with continued dose escalation until response was observed. Maintenance treatment continued at every 2-week intervals at the same dose at which response occurred. Protocol amendments increased the initial dose of DOXIL up to 40 mg/m<sup>2</sup>, with maintenance doses ranging from 10 to 40 mg/m<sup>2</sup>.

This study demonstrated the safety and efficacy of DOXIL at doses of 10 and 20 mg/m<sup>2</sup> administered at 2-week intervals. Objective response (complete or partial) response was reported in 81% of patients. Responses occurred rapidly, with a mean time to response of 57 days (or three cycles). Response was maintained for an average of 17 weeks, ranging up to 65 weeks. When compared to baseline, an overall reduction in lesion size as well as clinically and statistically significant reduction in nodularity and edema was reported along with the patients' best response to DOXIL. In addition, statistically significant numbers of patients experienced improvement in quality of life within the first six weeks of study, at the time of best AIDS-related KS response, and for the duration of the response.

### **Study 30-05**

Study 30-05 investigated the pharmacokinetics of DOXIL and conventional doxorubicin in patients with AIDS-related KS. Other objectives of the study included comparison of concentrations of doxorubicin within AIDS-related KS lesions following intravenous administration of each drug and to assess safety and tolerability of DOXIL. This randomized, single dose, crossover study, with optional long-term DOXIL maintenance therapy, enrolled 18 patients. Both DOXIL and conventional doxorubicin were administered in doses of 10, 20, and 40 mg/m<sup>2</sup>. Patients were treated for 2 cycles, with a 3-week interval between each cycle. Either DOXIL or conventional doxorubicin was administered in the first cycle, followed by the alternate drug in the second cycle, with a 4-week follow-up period. This study was conducted between January 1992 and June 1993.

Plasma samples for pharmacokinetic analyses were collected for 4 days following administration of the first dose of study drug. At 72 hours post-infusion, a representative KS lesion was excised from each patient and tissue

drug levels were measured. Disposition kinetics for the two drugs were markedly different. Disposition of doxorubicin after DOXIL administration occurred in two phases: a relatively short first phase of doxorubicin disposition accounted for only a small percentage of the area under the curve (AUC), with a long second-phase representing nearly 88% of the AUC. The second disposition half-life of DOXIL was 43.7, 35.8, and 38 hours in the 10, 20, and 40 mg/m<sup>2</sup> dose groups, respectively. Due to the rapid clearance of doxorubicin from plasma in patients treated with conventional doxorubicin, plasma concentrations of doxorubicin were below the limit of quantitation of the HPLC assay at all but the first time point after drug administration, and data could not be fitted to a pharmacokinetic model. The first disposition half-life of administration of conventional doxorubicin, representing the majority of the AUC, is reported to be less than 10 minutes. The volume of distribution of DOXIL (3.2-3.5 L/m<sup>2</sup>) was near the estimated plasma volume, indicating disposition of pegylated liposomal-encapsulated doxorubicin is controlled by the distribution of the liposome carrier. The volume of distribution of conventional doxorubicin is reported to be more than 500-times the plasma volume.

DOXIL disposition kinetics were reported to be independent of dose, and dose-dependent linear increases were observed in the initial plasma drug level (C<sub>max</sub>) and in AUC. Doxorubicinol, the major metabolite of doxorubicin, was not detected in plasma after DOXIL administration. Doxorubicin levels in biopsies of KS lesions from patients who received the same dose of DOXIL or conventional doxorubicin were 5 to 11-fold higher in the DOXIL-treated patients 72-hours after drug administration.

### **Study 30-10**

Study 30-10 was a Phase 3 prospectively randomized, parallel multicenter comparative study of DOXIL vs. Adriamycin, Bleomycin, and Vincristine (ABV) in the treatment of severe AIDS-related KS conducted at 25 U.S. sites between April 1993 and December 1994. In this study, 258 patients with moderate-to-severe AIDS-related KS were randomized to treatment with either DOXIL (133 patients) or ABV (125 patients). Patients were treated with either DOXIL 20 mg/m<sup>2</sup> or ABV (20 mg/m<sup>2</sup> Adriamycin, 10 U/m<sup>2</sup> bleomycin, and 1.0 mg/m<sup>2</sup> vincristine) at every 2-week intervals. All but 3 patients were male, and the median age was 38 years. The study report was submitted as part of an efficacy supplement in 1996.

Objective responses (complete and partial) responses were reported in 46.2% of DOXIL-treated patients, compared to 25.6% of ABV-treated individuals (P<0.001). In addition, DOXIL-treated patients improved in all nine domains of a self-administered Quality of Life questionnaire, and DOXIL-treated patients recorded significantly better scores in five domains (general health, pain, social functioning, energy level, and health distress).

Dose delays and dose modifications were more frequent in the ABV-treated group, with 46 (36.8%) of the 125 ABV patients terminating treatment prematurely due to an adverse event, compared to adverse event-related early termination in 14 (10.5%) of the 133 DOXIL-treated patients. Neuropathy, nausea and vomiting, and alopecia occurred more frequently with ABV treatment (28.0% vs. 12.0%, 57.6% vs. 33.8%, and 42.4 vs. 11.3% respectively). Mucositis was more common in the DOXIL-treated patients (18.0% vs. 8.0%). While neutropenia occurred in both treatment groups, ANC < 500/mm<sup>3</sup> was more common in the ABV-treated patients (13.6% vs. 6.0%).

More DOXIL-treated patients (68.0% vs. 34.0%) completed the six cycles of therapy. The difference in attrition was thought to be due to improved tolerance and efficacy of DOXIL over ABV.

### **Study 30-11**

Study 30-11 was a Phase 3 prospectively randomized, parallel, multicenter comparative study of DOXIL vs. Bleomycin and Vincristine (BV) in the treatment of AIDS-related KS conducted in Europe (17 sites) and the U.S. (5 sites) between January 1993 and September 1995.

A total of 241 patients with moderate-to-severe AIDS-related KS were enrolled in this study, with 121 patients randomized to treatment with DOXIL and 120 patients randomized to the BV arm. All but 2 of the patients were male, with a mean age of 38 years. Demographics and baseline disease characteristics were well balanced between the two treatment groups.

Patients were treated with either DOXIL (20 mg/m<sup>2</sup>) or BV (Bleomycin 15 U/m<sup>2</sup> and Vincristine 1.4 mg/m<sup>2</sup> (maximum dose 2.0 mg) at 3-week intervals. Objective responses (complete and partial) responses were reported in 58.7% of DOXIL-treated patients compared to 23.3% of BV-treated individuals (P<0.001).

Patients were asked to complete two quality of life questionnaires. With the Wu instrument (What is this?? Wayne/Aby/Alex?), DOXIL-treated patients improved significantly in the domains of cognitive functioning, overall quality of life, and health transition, while BV-treated patients were reported to have improvement in only the health distress domain. With the AIDS-related KS questionnaire, statistically significant improvement was reported for DOXIL-treated patients with regard to ease of walking, relief from sleep disturbance, and social well-being. On the other hand, when compared with baseline assessments, BV-treated patients reported significant improvement in social-well being only.

More DOXIL-treated patients (55.4% vs. 30.8%) were able to complete the six cycles of therapy specified in the protocol. More BV-treated patients discontinued the study prematurely as a result of adverse events (26.7% vs. 10.7%). Dose delays due to adverse events were more common in the DOXIL-treated patients (8.5% vs. 2.7%). Almost all patients (96.7% of DOXIL-treated and 95.8% of BV-treated patients) reported at least one adverse event. More adverse events were thought to be related to drug in the BV group than in the DOXIL group (21.1% vs. 10.0%), although the majority of adverse events were considered to be unrelated to study drug (68.1% for DOXIL-treated patients, 52.6% for BV-treated patients).

Nausea and vomiting (mostly of mild or moderate severity) was noted as an adverse event for both drugs (15.7% with DOXIL, 25.0% with BV). Treatment with BV was associated with more peripheral neuropathy (in 26.7% of BV-treated patients vs. 8.3% of those treated with DOXIL). Significantly more patients discontinued treatment prematurely in the BV group (69.2%) compared to the DOXIL group (44.6%) ( $P < 0.001$ ).

### **Study 30-12**

Study 30-12 was a Phase 3 non-comparative open-label multicenter study of DOXIL at a dose of 20 mg/m<sup>2</sup> administered at 3-week intervals to evaluate the safety and efficacy of long term DOXIL treatment in patients with moderate-to-severe AIDS-related KS. Treatment continued until disease progression or intolerance occurred. This study was conducted between March 1993 and December 1995 at 18 sites (12 U.S., 3 U.K., 2 Germany, and 1 The Netherlands). There was no fixed limit on the number of patients. Patients were eligible for enrollment if they were enrolled previously on a completed DOXIL study or if they were a treatment failure from a non-DOXIL based regimen. A total of 892 patients were enrolled in this study.

DOXIL was administered at a dose of 20 mg/m<sup>2</sup> at q 3-week intervals for a total of up to 20 cycles (the cumulative number of cycles included previously administered DOXIL in other studies). The 892 patients remained in the study for a duration ranging from 1 to 791 days (median: 127 days), with cumulative doses of DOXIL ranging from 3.3 to 769.7 mg/m<sup>2</sup> (median 120.0 mg/m<sup>2</sup>).

The pattern of adverse events noted in this study is similar to that noted in other DOXIL-AIDS-related KS studies.

Subsequently, a cohort of 77 patients was identified retrospectively as either having developed disease progression while undergoing systemic chemotherapy with a non-DOXIL based regimen or being intolerant to such therapy. The median CD4 counts for these individuals was only 10 cell/mm<sup>3</sup> and forty-nine of these 77 individuals (64%) had been previously treated with conventional doxorubicin. Using ACTG staging criteria, 78% of the patients were considered poor risk due to tumor burden, 96% were at poor risk due to immune system status, and 58% were at poor risk for systemic illness at baseline. All 77 patients had cutaneous or subcutaneous lesions, 40% also had oral lesions, 26% had pulmonary lesions, and 14% had gastrointestinal lesions as well. The majority of these individuals had disease progression while undergoing treatment with prior systemic chemotherapy.

The median time on study for these 77 patients was 155 days (range 1 to 456 days) and the median cumulative dose was 154 mg/m<sup>2</sup> (range 20 to 620 mg/m<sup>2</sup>).

Two analyses were used to evaluate efficacy of DOXIL in these patients. The primary analysis relied on objective and fully quantifiable changes in the characteristics of five indicator lesions. The secondary analysis relied on the investigator's assessment of the effect of therapy on the patient's disease over the entire body. The investigator's assessment of response was based on ACTG criteria, defining a partial response as no new lesions, sites of disease, or worsening edema, flattening of  $\geq 50\%$  of previously raised lesions, or the area of indicator lesions decreasing by  $\geq 50\%$ , and maintenance of response for at least 21 days. The other method of assessment of response was indicator lesion assessment of up to 5 prospectively identified representative indicator lesions, defining a partial response as flattening of  $\geq 50\%$  of previously raised indicator lesions or  $\geq 50\%$  decrease in the area of the indicator lesions lasting at least 21 days with no prior progression.

Only patients with adequate documentation of baseline and follow-up assessments were considered evaluable for response. Patients treated concomitantly for their AIDS-related KS, those who had undergone local radiotherapy to sites encompassing 1 or more of the indicator lesions within 2 months prior to study entry, those who had less than 4 indicator lesions, or those who had less than 3 raised indicator lesions at baseline (for indicator lesion assessment only) were considered inevaluable for response.

Of the 77 patients with disease progression while undergoing treatment with prior systemic non-DOXIL based chemotherapy or those intolerant to such therapy, 34 were evaluable for investigator assessment of response, and 42 were evaluable for indicator lesion assessment. By investigator assessment, partial responses were observed overall in 27% of the patients (n=34), with a median duration of response of 73 days (range 42-210 days); and in those (n=20) who had been treated previously with doxorubicin, partial responses were reported in 30%, with a median duration of response of 89 days (range 42-210 days).

For response by indicator lesion assessment, partial responses were observed overall in 48% of the patients (n=42), with a median duration of response of 71 days (range 22-210 days); and in those (n=23) who had been treated previously with doxorubicin, partial responses were reported in 52%, with a median duration of response of 79 days (range 35-210 days).

**Table 3** summarizes the results of Study 30-12.

**Table 3: Study 30-12: Response in Refractory<sup>a</sup> AIDS-Related KS Patients**

<b>Investigator Assessment</b>	<b>All Evaluable Patients (n=34)</b>	<b>Evaluable Patients Who Received Prior Doxorubicin (n=20)</b>
<b>Response<sup>b</sup></b>		
Partial (PR)	27%	30%
Stable	29%	40%
Progression	44%	30%
<b>Duration of PR (days)</b>		
Median	73	89
Range	42–210	42–210
<b>Time to PR (days)</b>		
Median	43	53
Range	15–133	15–109

  

<b>Indicator Lesion Assessment</b>	<b>All Evaluable Patients (n=42)</b>	<b>Evaluable Patients Who Received Prior Doxorubicin (n=23)</b>
<b>Response<sup>b</sup></b>		
Partial (PR)	48%	52%
Stable	26%	30%
Progression	26%	17%
<b>Duration of PR (days)</b>		
Median	71	79
Range	22–210	35–210
<b>Time to PR (days)</b>		
Median	22	48
Range	15–109	15–109

<sup>a</sup> Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

<sup>b</sup> There were no complete responses in this population.

### Study 30-14

Study 30-14 was a randomized, cross-over, pharmacokinetic and tumor localization study in which DOXIL was administered as either 10- and 20 mg/m<sup>2</sup> in order to assess the relationship between dose and pharmacokinetic variables. In this single center study conducted between March and December 1993, 43 patients with AIDS-related KS were treated with 2 cycles of DOXIL at 3-week intervals. The first 26 patients were randomized to treatment with either the 10 or 20 mg/m<sup>2</sup> dose, followed 3 weeks later with crossover to the other dose. Plasma samples for plasma pharmacokinetic analyses were collected for 4 days following the first dose. At 48-hours post-infusion, a representative KS lesion was excised and tissue drug levels were measured. The protocol was amended in September 1993 to include 16 additional patients who were randomized to treatment with either

the 10 or the 20 mg/m<sup>2</sup> dose level, followed by biopsy of KS lesions and normal skin at either 48 or 96 hours post-infusion. These additional individuals were not crossed over to the alternate dose and they did not undergo full plasma pharmacokinetic analyses.

In general, both dose levels of DOXIL were well tolerated. DOXIL displayed linear pharmacokinetics, best described by a two-compartment model. Plasma concentrations and AUCs were dose-proportional, whereas DOXIL disposition kinetics were independent of dose. Following DOXIL administration, disposition occurred in two phases, with a relatively short first phase ( $\lambda_1$  half-life of 5 hours) and a prolonged second phase ( $\lambda_2$  half-life of 52 hours) that accounted for the majority of the AUC. Very low levels of doxorubicinol, the major metabolite of doxorubicin, were detected in plasma after dosing, representing approximately 0.1% - 0.5% of the measured doxorubicin plasma levels. Since only non-liposomal doxorubicin is metabolized, and since doxorubicinol levels are typically one-half of the doxorubicin levels, this suggests that the amount of free, non-liposomal doxorubicin in the plasma is less than 1% of the total.

Forty-eight hours after DOXIL administration, median doxorubicin levels in biopsies of KS lesions were 2-fold (for the 10 mg/m<sup>2</sup> dose) and 20-fold higher (for the 20 mg/m<sup>2</sup> dose) than in normal skin from the same patient. Doxorubicin levels in the KS lesions 96-hours after treatment were 3-times (for the 10 mg/m<sup>2</sup> dose) and 4-times (for the 20 mg/m<sup>2</sup> dose) greater than in normal skin, demonstrating the selective accumulation of DOXIL in AIDS-related KS lesions at the 20 mg/m<sup>2</sup> dose.

### **Study 30-21**

Study 30-21 compared the effects of DOXIL and non-liposomal (conventional) doxorubicin on myocardial tissue. Between July 1994 and July 1995 ten patients with AIDS-related KS who had been treated with >400 mg/m<sup>2</sup> (469 to 860 mg/m<sup>2</sup>) of DOXIL underwent myocardial biopsy. For each DOXIL patient, a matched doxorubicin patient who had received a similar cumulative amount of doxorubicin was identified from a cardiac biopsy database of 131 patients who had undergone cardiac biopsy while participating in clinical studies at Stanford University from 1974-1982.

DOXIL was administered at a dose of 20 mg/m<sup>2</sup> at 2-3 week intervals. Individuals treated with conventional, non-liposomal doxorubicin were treated at a dose intensity of 20 mg/m<sup>2</sup> per week on one of two schedules: 20

mg/m<sup>2</sup> every week or 60 mg/m<sup>2</sup> every 3 weeks. DOXIL-treated patients had not been treated previously with any other anthracycline.

The primary criterion for match was cumulative doxorubicin exposure within 10 mg/m<sup>2</sup>. Using a 7-point morphologic grading system for cardiotoxicity, the amount of cardiac damage in the DOXIL- and doxorubicin-treated patients was measured and compared.

The primary criterion for evaluation was the condition of the myocardium as assessed by the Billingham Morphologic Grading System for Cardiotoxicity. This scale begins at Grade 0 (cells show no anthracycline damage) and progresses to Grade 3.0 (specimens exhibit diffuse cell damage, with more than 35% of cells showing pathologic change, loss of contractile elements and organelles, and mitochondrial and nuclear degeneration).

Less myocardial damage was observed in patients treated with DOXIL compared to their matched doxorubicin controls. The mean (+/-SD) cardiac biopsy score for the DOXIL-treated patients was 0.5 (+/-0.55), (range 0-1.5) compared to a mean of 2.4 (+/-0.70) (range 1.5-3.0) for the unadjusted conventional doxorubicin patient and a mean of 1.8 (+/-0.78) (range 0.7-3.0) for the adjusted doxorubicin patient. The difference between the DOXIL and doxorubicin patients was statistically significant (P <0.001) when the biopsy scores for the DOXIL-treated patients were compared with the unadjusted scores for the doxorubicin-treated patients. The same test comparing the DOXIL patient scores with the doxorubicin patient scores adjusted for administered dose also resulted in a significant difference (p=0.015).

DOXIL<sup>®</sup> (doxorubicin HCl liposome injection) is doxorubicin HCl formulated as a pegylated liposome which alters the plasma pharmacokinetics of the parent drug. An advantage of DOXIL is that the cardiac biopsy studies show that patient treated with DOXIL in cumulative doses above 360 mg/m<sup>2</sup> show significantly less myocardial damage than in patients treated with similar or less cumulative doses of conventional doxorubicin.

### **Study 30-24**

Study 30-24 was a Phase 3 open-label multicenter study of long-term use of DOXIL in the treatment of moderate-to-severe AIDS-related KS that was conducted in Europe and enrolled 94 patients between February 1994 and October 1998. Patients treated previously on a DOXIL protocol within the last 4 months and who had AIDS-related KS of a severity requiring systemic

chemotherapy were eligible for enrollment if no other treatment option was available. DOXIL was administered at a dose of 20 mg/m<sup>2</sup> at 3-week intervals for a cumulative total of up to 20 cycles, with an option for extension of treatment upon Sponsor approval. Six patients were classified as complete responders.

Overall, a total of 1,083 doses of DOXIL were administered to 94 patients, and the median number of days on study drug was 191 (range 1-1,645 days). The median cumulative dose of DOXIL was 146.7 mg/m<sup>2</sup> (range 20.0 – 1,060.9 mg/m<sup>2</sup>). Most of the patients (86 of 94, 91.5%) reported at least one adverse event, and 16 (17%) patients reported adverse events that were probably related to study drug and 46 (48.9%) reported adverse events that were possibly related to study drug, and 81 (86.2%) reported adverse events that were unrelated to study drug. Sixty-one of the 94 patients reported a severe adverse event. The most frequently reported adverse events were pneumonia (16 patients, 17.0% - not related to study drug), neutropenia (15 patients, 16.0% - related to study drug), and leukopenia (14 patients, 14.9% - related to study drug).

A total of 60 study patients died. Forty-seven of the deaths were on study and 13 patients died during the follow up period. The majority of deaths were due to other AIDS-related complications (n=42) and progression of AIDS-related KS (n=11). The median time to death was 337 days from the start of study drug (range 6+ to 1,708+ days). Death of one patient from sepsis was considered possibly related to study drug, and for the remaining 59 patients, death was considered unrelated to study drug.

### **Study 30-25**

Study 30-25 was a Phase 3 multicenter non-comparative open-label study of DOXIL in the treatment of patients with moderate-to-severe AIDS-related KS who had no other treatment options, were intolerant to non-DOXIL based combination chemotherapy, or who had been enrolled in another DOXIL protocol and for whom continuation of DOXIL was medically indicated. This study was conducted between December 1994 and January 1996, enrolling 635 patients.

DOXIL was administered at a dose of 20 mg/m<sup>2</sup> at 3-week intervals. The overall incidence of objective response (complete and partial) was 16.4% (104/635). Three (0.5%) patients were classified as complete responders, and 101 (15.9%) were recorded as having a partial response. The median duration of response was 219.0 days (range 29+ to 327+ days).

In total, 4,309 doses of DOXIL were administered to the 635 patients, and the duration of DOXIL therapy ranged from 1.0 – 367.0 days, with a median of 117.0 days. The median cumulative dose of DOXIL was 120.0 mg/m<sup>2</sup> (range 10.3 to 443.8 mg/m<sup>2</sup>). A total of 437 adverse events were reported by 255 (43.4%) of the 588 patients with AE forms. Of these, 112 (19.0%) experienced mild events, 130 (22.1%) experienced moderate events, and 86 (14.6%) experienced severe adverse events. Adverse events considered possibly related and probably related to DOXIL were reported in 192 (32.7%) and 107 (18.2%) patients, respectively. The Adverse Event form used in this study listed four categories of severity (mild, moderate, severe, and fatal), and two categories of relationship of the adverse event to study drug (possibly related and probably related).

The most common adverse events reported were leukopenia (119 patients, 20.2%), asthenia (32 patients (5.4%), anemia 26 patients (4.4%), and nausea (25 patients, 4.3%). Leukopenia was the most frequently reported serious adverse event (62 patients, 10.5%), followed by anemia (9 patients, 1.5%).

A total of 176 (27.7%) of study patients died (156 on study, and 20 died during the follow-up period). The majority of deaths (n=153) were due to HIV-related opportunistic disease. The median time to death was 366 days from the start of study drug (range 1+ to 616+ days). Overall, long-term use of DOXIL was well tolerated in this patient population.

### **Study 30-26**

Study 30-26 was another long-term Phase 3 open-label multicenter study conducted at 5 sites in Germany between April 1995 and February 1996 to provide DOXIL to patients with AIDS-related KS for whom no other therapy was available. Administration of up to 20 cycles of DOXIL, 20 mg/m<sup>2</sup> at q 3-week intervals, was permitted. A total of 67 patients with AIDS-related KS were treated with 349 doses of DOXIL, with at least 1 clinical response recorded. The median number of days on study drug was 95 (range 1.0 to 231.0 days). The median cumulative dose was 99.8 mg/m<sup>2</sup> (range 10.0 to 241.1 mg/m<sup>2</sup>). The mean time to death was 177.9 days (range 1+ to 447+ days).

## **3.5. Non Company-Sponsored Studies**

### **DOXIL plus HAART versus HAART alone in AIDS-Related KS**

This investigator-initiated study conducted in Spain was a randomized, open-label, multicenter study comparing DOXIL plus HAART versus HAART alone in 28 patients naïve to, or failing HAART with moderate-advanced

Kaposi's sarcoma This study was designed to compare the evolution of AIDS-related KS in patients with HIV receiving DOXIL and HAART to those receiving HAART alone.

Patients had to have 10 or more visceral, mucosal or cutaneous lesions. Life-threatening AIDS-related KS was an exclusion criterion. Patients were randomized in a 1:1 fashion to treatment with DOXIL (20 mg/m<sup>2</sup> every 3 weeks) plus HAART or HAART alone. Patients who progressed or did not respond to HAART alone were considered non-responders and permitted to receive DOXIL. The primary study endpoint was objective response rate.

Patients in the DOXIL plus HAART-treated group were predominately male (92%) and the median age was 41 years (range 35 to 47 years). Median CD4 count was 79 cells/mm<sup>3</sup> (range 22-206). Patients in the HAART alone-treated were male (100%) and the median age was 40 (range 33-45). Median CD4 count was 180 cells/mm<sup>3</sup> (range 33-231). Demographic characteristics were well balanced between groups.

The response rate for the DOXIL plus HAART cohort was 76% (10/13) and 20% (3/15) for the HAART alone cohort (*P*=0.003). **Table 4** below presents a summary of the response rates. Ten of the 15 patients in the HAART alone-treated group went on to receive DOXIL. In nine patients, AIDS-related KS progression was identified prior to treatment with DOXIL. Seven of these patients progressed within the first 3 months on study. Two patients had a delayed progression between 5 and 6 months and 1 patient had no amelioration observed after 9 months of HAART. In the 10 patients that crossed over to DOXIL, 8 achieved a complete response.

<b>Table 4: Response Rates (Spanish Study)</b>		
	HAART N = 15	DOXIL + HAART N = 13
HAART Naïve	80%	77%
Response Rate (48 weeks) (95% CI)	20% (4.3, 48.1)	76%* (46.2, 95)

\**P* = 0.003

Adverse events were reported in 33% of patients treated with DOXIL. Anemia, and neutropenia were most common (n=3). Other adverse events included mucositis (n=2), fever, hepatotoxicity, and enteritis (n=1). Most of these events were mild and did not result in treatment interruption. Three patients had dose reductions. Two patients died while on DOXIL, but death

was assessed as not related to AIDS-related KS or study drug (see **Attachment 2**).<sup>1</sup>

### **DOXIL & HAART Treatment & CD4+ Counts in AIDS-Related KS**

This match-control study included 54 HIV-1-infected patients with KS compared to 54 non-KS HIV-1-infected patients, matched for age, sex, CD4+ T cell counts ( $\pm 25\%$ ), HIV RNA load ( $\pm 25\%$ ), and previous antiretroviral therapy for immunological and virological treatment responses. This study was conducted in 5 centers in Germany between 1997 and 2002. The primary endpoint was immune reconstitution.

Patients with confirmed HIV-1 infection and a proven diagnosis of KS were sequentially included. All patients received HAART and this study allowed for patients with all stages of KS. Eligibility also took into account treating physician's judgment to start treatment, based on the patient's immunological and virological status, dissemination and severity of the disease as well as the likelihood of response to alternative treatments. Patients received DOXIL at 20 mg/m<sup>2</sup> every 2 weeks for at least 6 cycles with the option to continue treatment if the patient was deriving benefit.

The effect of DOXIL on HAART-mediated immune reconstitution and viral suppression can be summarized as follows. Assessment of the 54 non-KS matched patients to the KS-matched patients showed that the absolute CD4+ T cell counts were essentially unchanged at the 3 and 6 month timeframe, despite decreases in the leukocytes counts for the patients receiving DOXIL and HAART compared to HAART alone. A significant decline in HIV-1 RNA viral load in both study patients and matched pairs was observed simultaneously to the increase in CD4+ T cell counts. Study patients and matched pairs did not differ significantly with regard to the proportion of patients with viral loads below the level of detection (<400 copies/mL) after 3 and 6 months of treatment.

Forty percent of patients treated with DOXIL, had been treated with HAART for more than 6 months prior to chemotherapy. Fifty-five percent had prior HAART exposure for a duration of less than 4 weeks, whereas 40% had HAART exposure for more than 6 months. The median number of cycles of DOXIL administered was 14. The majority (81.5%) of patients responded to treatment with 55% and 26% of patients achieving a partial and complete response respectively. Best clinical responses were observed at a median of 8 weeks. Eighteen percent of patients were required to receive additional KS

treatment interventions after discontinuing DOXIL. A univariate analysis did not identify any factors predictive of response.

Hematologic adverse events were more common in study patients than matched-pairs, with severe (level 4 according the WHO) hematologic adverse events in 2 study patients. Hepatic toxicity was more common in the study patients (22%) compared to (4%) in the matched-pair group. Mild cardiotoxicity was observed in 4 patients (7.4%), all in the study group. Severe polyneuropathic complaints occurred more frequently in the study group (7.4%) (see **Attachment 3**).<sup>16</sup>

#### **4. DIFFICULTIES ENCOUNTERED IN CONDUCT, ACCRUAL OR COMPLETION OF STUDIES**

The sponsor has given substantial consideration to the conduct of an additional randomized study that might demonstrate clinical benefit. Based on the totality of the data previously submitted including Study 30-38 and the two recent publications that support the clinical benefit of DOXIL in patients with AIDS-related KS receiving HAART above and beyond the benefits that may be achieved by HAART alone, we believe that it would be difficult if not impossible to conduct a randomized clinical study in patients with AIDS-related KS. These challenges are described below.

- **Published Literature:** The recent Spanish and German studies supports the clinical benefit of DOXIL in patients with AIDS-related KS. The randomized study in Spain of DOXIL plus HAART compared to HAART alone shows the superiority of the combination over HAART alone, including after crossover of patients from the HAART alone-arm to the combination when appropriate. The German study reports results similar in magnitude to the Spanish study.

The recent publication of an algorithm for the treatment of AIDS-related KS (see **Attachment 4**)<sup>20</sup> illustrates current advice provided for these patients and highlights that the recommendation is to use HAART and a liposomal anthracycline to treat patients who progress while on HAART or who have advanced or life-threatening disease. We think that the acceptance of this treatment paradigm, and the data on which it is based, underlie the difficulty of conducting another randomized study of HAART versus HAART and DOXIL for the treatment of AIDS-related KS.

In light of this information of the consistency of the results reported in the Study 30-38, the Spanish and German studies, we believe it would be

inappropriate to conduct another study where a proportion of patients would be randomized to receive less than the standard of care for their condition.

- **DOXIL is the preferred therapy:** DOXIL is commercially available in multiple countries, approved in over 70 countries for this disease, and is regarded as the preferred first-line treatment of AIDS-related KS when systemic chemotherapy is appropriate. Currently 70% of patients with AIDS-related KS in the US are treated with DOXIL because of the benefit that has been observed. The acceptance of DOXIL as well as the widespread use of HAART, make it very difficult to do a meaningful study that would provide additional useful information above that which we have already obtained through clinical studies and reported in published literature.<sup>13</sup> DOXIL is the appropriate comparator in any study and randomization to another agent may not be appealing to patients, doctors and IRBs.
- **Incidence of AIDS-Related KS:** The widespread use of HAART has resulted in a markedly decreased overall incidence of AIDS-related KS. It will be challenging to achieve enrollment targets with the low incidence of AIDS-related KS in the United States and most developed countries.

It should be noted that the Spanish study enrolled 28 patients between 2000 and 2003 and the German study enrolled 54 patients between 1997 and 2002.

- **HAART utilization:** Patients who present with AIDS-related KS are treated with HAART and DOXIL concomitantly when there is a need to achieve rapid cytoreduction, because of AIDS-related KS lesions that are life-threatening, symptomatic or cosmetically disfiguring. Regression of AIDS-related KS may take 3-9 months after the initiation of HAART alone as a consequence of viral suppression and immune reconstitution, but with DOXIL the median time to response was 30 days (range 14-82) in Study 30-38.<sup>19</sup> Protocols that require patients to have documented sustained suppression of viral replication for a long pre-specified period (6-18 months) prior to enrollment into a study evaluating the safety and efficacy of new AIDS-related KS agents in order to differentiate between the impact of HAART and the activity of DOXIL, will result in a significant reduction in the numbers of eligible AIDS-related KS patients.

- **Confounding Impact of HAART Therapy on Interpretation of Data:** As discussed earlier, the changes in antiretroviral therapy that occurred immediately prior to or during the conduct of Study 30-38 were felt by FDA to confound their ability to adequately assess the effect of DOXIL on AIDS-related KS. As the widespread clinical acceptance and use of HAART did not begin until after Study 30-38 had initiated, the impact of HAART on subjects enrolled in 30-38 was not taken into account when designing the original study.

This issue however still exists in that many patients with AIDS-related Kaposi's sarcoma who require systemic chemotherapy also may require modification of HAART for reasons of efficacy or safety, further complicating their eligibility for a pivotal study or their continued participation in that study. When patients fail one combination, they will receive additional drugs, or a new combination, novel or new investigational anti-retroviral agents, all of which will be concurrent with DOXIL administration. These treatments may confound the interpretation of clinical benefit of DOXIL in any study of patients with AIDS-related Kaposi's sarcoma such that the challenges faced by FDA in their review of Study 30-38 will likely be repeated.

- **Ethical considerations:** Ethical considerations and patient concerns/acceptance make it extremely difficult to conduct a controlled study in this patient population in the US. Delay of an active therapy of AIDS-related KS is not an acceptable option to either patients or treating physicians. Furthermore, as DOXIL is regarded as the preferred first-line therapy for patients with AIDS-related KS for whom systemic chemotherapy is medically indicated, including in patients receiving HAART, it may be equally as difficult to conduct a study utilizing a "second choice" agent as a comparator.

## 5. CONCLUSION

J&JPRD believes that we have shown due diligence in attempting to address our Phase 4 commitment for DOXIL in AIDS-related KS. We believe that the totality of the data presented provide substantial evidence for the clinical benefit of DOXIL in patients with AIDS-related KS. We remain eager to work with the Agency to ensure the product remains accessible to this small but highly important patient population.

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