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Background Information Regarding Accelerated Approval of DOXIL® in Kaposi's Sarcoma

Phase IV Commitments

DOXIL® (doxorubicin HCl liposome injection)
NDA No 50-718

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Background Information Regarding Accelerated Approval of DOXIL® in Kaposi's Sarcoma

PHASE IV COMMITMENTS

1. SUMMARY

DOXIL® (doxorubicin HCl liposome injection) received accelerated approval on 17 November 1995 for the treatment of chemotherapy refractory AIDS-related Kaposi's sarcoma (AIDS-KS). This approval was based on objective tumor response rates from an interim analysis of an open-label, single-arm, multicenter study. The original phase IV commitment trial (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®" was designed in close collaboration with the FDA. On 31 July 2002, the FDA communicated to the Sponsor that the introduction of highly active antiretroviral therapy for the treatment of HIV infection during the conduct of the trial made it difficult for the FDA to interpret the clinical benefit of DOXIL. This resulted in the non-approval of the supplemental New Drug Application. Discussions are underway between the Sponsor and the FDA to design another phase IV commitment study that will allow for the conversion from accelerated approval to full approval for this indication.

To date, it is estimated that more than 7000 patients with AIDS-KS in the United States have received treatment with this drug product (doxorubicin HCl liposome injection). DOXIL is considered the standard of care for US patients with AIDS-KS for whom systemic chemotherapy is indicated. More than 20 manuscripts have been published regarding the use of doxorubicin HCl liposome injection (DOXIL®) in the treatment of patients with AIDS-KS.

2. GENERAL INFORMATION

Drug Name: DOXIL® (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 trials 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

3. INTRODUCTION

3.1. Overview of AIDS-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), 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.[1]

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 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, impacting the patient's overall quality of life. Gastrointestinal involvement has been noted in approximately 40% of patients at initial diagnosis of AIDS-KS and in up to 80% of patients with AIDS at autopsy. 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. KS visceral lesions may be present in patients who have no cutaneous manifestations. Palliation of symptoms is a major goal of KS treatment.[2]

The incidence of AIDS-KS in the United States has declined since its peak in the late 1980's to approximately 0.7 cases per 100,000 population in 1999.[3,4] This decline was evident before the introduction of HAART. The frequency of KS as a presenting AIDS illness among the Multicenter AIDS Cohort Study (MACS) has declined from 25.6 cases per 100 patient-years in the early 1990's to 7.5 cases per 100 patient-years in 1996-1997.[5] The CDC reported a decline in KS incidence by 8.8% per year from 1990 through 1998. Nonetheless, new cases of KS continue to present, even among patients with viral load suppression resulting from treatment with

antiretroviral therapy.[6,7] Despite the low incidence of KS, considerable morbidity and mortality still exist in patients with AIDS who develop KS.

Management and treatment options for AIDS-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.[2] Some patients with AIDS-KS have experienced lesion regression after initiation of triple-drug antiretroviral therapy. Optimal antiretroviral therapy may inhibit development or progression of KS in several ways, including treatment of the underlying immunosuppression.

AIDS-KS treatment can be broadly classified into local or systemic therapy.

Local therapy directed at control of individual lesions is appropriate for limited, relatively slowly progressive disease without life-threatening organ involvement. Local approaches are most appropriate for individuals with few numbers of 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. Because local treatment does not result in a cure, the most important goals are to improve the patient's appearance and reduce the suffering and social isolation AIDS-KS can cause.[2,8,9,10]

Systemic chemotherapy is medically indicated for individuals with advanced or rapidly progressive AIDS-KS that causes medical or functional impairment.[10] 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-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. Response rates of 10% to 48% have been reported with single agent cytotoxic agents including doxorubicin, bleomycin, and vincristine, with higher response rates (56% to 88%) when

used in combination.[10] (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 II 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 II 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-KS, treatment with one of the FDA-approved liposomal anthracyclines is the current standard of care for first-line therapy of AIDS-KS. [2, 8, 9]

Before the approval of DOXIL for this patient population, combination cytotoxic chemotherapy with bleomycin and vincristine (BV) or doxorubicin (Adriamycin®), bleomycin and vincristine (ABV) was considered to be the most effective chemotherapy for AIDS-KS, with reported response rates of 60 to 80%, but with appreciable toxicity. The initial clinical studies of ABV in AIDS-KS generally administered doxorubicin at doses of either 40 mg/m^2 every 4 weeks or 20 mg/m^2 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.[2,8,9] While many patients benefited from such agents and regimens, it was not infrequent for patients to die with severe, progressive AIDS-KS in spite of optimal therapy.

DOXIL, a pegylated liposomal formulation of doxorubicin, was developed to circumvent the short *in vivo* half-life of standard doxorubicin and has been investigated extensively in patients with AIDS-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 thereby increasing plasma residence time. Because of the slower plasma clearance of DOXIL relative to conventional doxorubicin, 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).[11] Such 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 KS lesions and normal skin were obtained from 11 patients at 48 and 96 hours following infusion of DOXIL at a dose of 20 mg/m^2. The doxorubicin concentration was 3- to 53-times (median 19) higher in the AIDS-KS lesions than in normal skin at 48 hours after the infusion.[12]

Superiority of single agent DOXIL has been reported in several studies comparing DOXIL monotherapy (20 mg/m^2 every 2 weeks) with combination chemotherapy regimens such as BV and ABV.[2,10]

DOXIL is generally well tolerated compared to other cytotoxic chemotherapy, with myelosuppression as the most common dose-limiting adverse event in patients with AIDS-KS. While neutropenia occurs most often, anemia and thrombocytopenia occur less frequently, as do nausea and vomiting and stomatitis. Palmar-plantar erythrodysesthesia 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. Primarily because of a superior safety profile and concomitant improvement in quality of life, single agent DOXIL has largely replaced combination regimens (ABV and BV) as the first-line systemic treatments of choice. In the period between September 2001 and August 2002, 61% of patients with AIDS-KS were treated with DOXIL monotherapy as their initial treatment. In that same time period, no other cytotoxic chemotherapy drug was used in more than 7% of this patient population.[13]

DaunoXome is a liposomal formulation of daunorubicin that has also demonstrated activity in AIDS-KS and was approved in 1996. In the pivotal trial, DaunoXome treatment resulted in an objective response rate that was similar to the control ABV arm (25% vs. 28%).[14] IMS Health 2002 year- to-date data identifies only limited usage of liposomal daunorubicin.[15] Paclitaxel was approved in 1997 for the treatment of chemotherapy refractory AIDS-KS. The side effect profile of paclitaxel is well known and includes significant myelosuppression and alopecia. Prolonged paclitaxel therapy can also cause peripheral neuropathy. In the period between September 2001 and August 2002, 6.6% of patients with AIDS-KS were treated with single agent paclitaxel as their initial treatment. Paclitaxel in

combination with etoposide (7.4%) or DOXIL (5.9%) also was reported as first-line therapy in patients with AIDS-KS.[15]

Since the introduction of HAART, few studies have been conducted to demonstrate a therapeutic benefit of cytotoxic chemotherapy in patients with AIDS-KS, even though the use of cytotoxic chemotherapy is the standard of care in this patient population with presentation of KS. Study 30-38 was a randomized trial of DOXIL vs. DaunoXome designed to demonstrate the clinical benefits of DOXIL in patients with AIDS-KS and was intended to convert the accelerated approval of DOXIL to full approval. This study was conducted between September 1996 and September 2000, during the timeframe of the introduction of HAART. The introduction of HAART confounded the ability to assess the clinical benefit of DOXIL on AIDS-KS. The number of patients for which HAART therapy did not confound the assessment of the clinical benefit of DOXIL was small and did not allow for an adequate FDA assessment for conversion of DOXIL to full approval for AIDS-KS.

Even with the low incidence of AIDS-KS, KS remains one of the most common neoplasms reported in patients with AIDS. New cases of KS continue to be diagnosed, even among patients with HIV viral load suppression, and 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 KS, especially those with symptomatic visceral disease, the rapid tumor reduction achieved with systemic chemotherapy, even in the face of a stable regimen of HAART, can be a lifesaving intervention.

3.2. History of DOXIL Clinical Development In AIDS-KS

DOXIL was granted accelerated approval on 17 November 1995 for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination therapy or in patients who are intolerant to such therapy.

Eleven studies have been conducted that evaluate the use of DOXIL in patients with AIDS-KS. These studies include 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).

More than 1700 patients with AIDS-KS were enrolled in 7 primary studies (30-03, 30-05, 30-10, 30-11, 30-12, 30-14 and 30-38) and in 3 long-term follow-up studies (30-24, 30-25 and 30-26). The majority of the patients were male, with patient ages ranging from 21-77 years (median + 38 years).

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

Table 1: DOXIL/Caelyx Clinical Trials in AIDS-KS Patients

Study No.	Design	Treatment, DOXIL Dose (mg/m2); Frequency	No. of pts.	Study Endpoints
30-03	Phase II/III, 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 I, 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 III, randomized, parallel, multicenter; comparison to ABV	20; every 2 weeks for up to 6 cycles	258	Compare objective response and safety
30-11	Phase III, randomized, parallel, multicenter; comparison to BV	20; every 3 weeks for up to 6 cycles	241	Compare objective response and safety
30-12	Phase III, 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 I, 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 I/II, 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 III, 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 III, 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 III, 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
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

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

[a] 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.

Study 30-03

Study 30-03, a Phase II/III 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-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 KS lesions, normal skin, and serum following treatment with DOXIL.

A total of 247 patients with AIDS-KS (and 1 non-AIDS-KS patient) were treated with DOXIL in cumulative doses ranging from 10-520 mg/m^2 in this open-label, multicenter, dose escalation study. DOXIL was to be administered every 2 weeks, initially at a dose of 10 mg/m^2, 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^2, with maintenance doses ranging from 10 to 40 mg/m^2.

This study demonstrated the safety and efficacy of DOXIL at doses of 10 and 20 mg/m^2 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 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-KS. Other objectives of the trial included comparison of concentrations of doxorubicin within AIDS-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^2. 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 PK 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^2 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^2) 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_{max}) 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 to11-fold higher in the DOXIL-treated patients 72-hours after drug administration.

Study 30-10

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

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 < $500/mm^3$ 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. 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 III prospectively randomized, parallel, multicenter comparative trial of DOXIL vs. Bleomycin and Vincristine (BV) in the treatment of AIDS-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-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^2) or BV (Bleomycin 15 U/m2 and Vincristine 1.4 mg/m^2 (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, 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 KS questionnaire, statistically significant improvement was reported for DOXIL-treated patients in regards 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 III non-comparative open-label multicenter study of DOXIL at a dose of 20 mg/m^2 administered at 3-week intervals to

evaluate the safety and efficacy of long term DOXIL treatment in patients with moderate-to-severe AIDS-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 rolled over from 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^2 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^2 (median 120.0 mg/m^2).

The pattern of adverse events noted in this study is similar to that noted in other DOXIL-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 $cell/mm^3$ 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^2 (range 20 to 620 mg/m^2).

Two analyses of tumor response were used to evaluate efficacy of DOXIL in these patients. Investigator 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 ≥50% of previously raised indicator lesions or ≥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 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 2 summarizes the results of 30-12.

Table 2: Study 30-12: Response in Refractory[a] AIDS-KS Patients

Investigator Assessment	All Evaluable Patients (n=34)	Evaluable Patients Who Received Prior Doxorubicin (n=20)
Response[b]		
Partial (PR)	27%	30%
Stable	29%	40%
Progression	44%	30%
Duration of PR (days)		
Median	73	89
Range	42–210	42–210
Time to PR (days)		
Median	43	53
Range	15–133	15–109
Indicator Lesion Assessment	**All Evaluable Patients (n=42)**	**Evaluable Patients Who Received Prior Doxorubicin (n=23)**
Response[b]		
Partial (PR)	48%	52%
Stable	26%	30%
Progression	26%	17%
Duration of PR (days)		
Median	71	79
Range	22–210	35–210
Time to PR (days)		
Median	22	48
Range	15–109	15–109

[a] Patients with disease that progressed on prior combination chemotherapy or who were intolerant to such therapy.

[b] 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^2 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-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^2 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^2 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 (λ_1 half-life of 5 hours) and a prolonged second phase (λ_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^2 dose) and 20-fold higher (for the 20 mg/m^2 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^2 dose) and 4-times (for the 20 mg/m^2 dose) greater than in normal skin, demonstrating the selective accumulation of DOXIL in KS lesions.

Study 30-21

Study 30-21 compared the effects of DOXIL and non-liposomal (conventional) doxorubicin on myocardial tissues. Between July 1994 and July 1995 ten patients with AIDS-KS who had been treated with >400 mg/m^2 (469 to 860 mg/m^2) 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 trials at Stanford University from 1974-1982.

DOXIL was administered at a dose of 20 mg/m^2 at 2-3 week intervals. Individuals treated with conventional, non-liposomal doxorubicin were treated at a dose intensity of 20 mg/m^2 per week on one of two schedules: 20 mg/m^2 every week or 60 mg/m^2 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^2. 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 patients. The same test comparing the DOXIL patient scores with the doxorubicin patient scores adjusted for administered dose also gave a significant difference ($p=0.015$).

Study 30-24

Study 30-24 was a Phase III open-label multicenter study of long-term use of DOXIL in the treatment of moderate-to-severe AIDS-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-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^2 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 1083 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^2 (range 20.0 – 1,060.9 mg/m^2). 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 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 III multicenter non-comparative open-label study of DOXIL in the treatment of patients with moderate-to-severe AIDS-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^2 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, 4309 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^2 (range 10.3 to 443.8 mg/m^2). 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 probable 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 III open-label multicenter study conducted at 5 sites in Germany between April 1995 and February 1996 to provide DOXIL to patients with KS for whom no other therapy was available. Administration of up to 20 cycles of DOXIL, 20 mg/m^2 at q 3-week intervals, was permitted. A total of 67 patients with AIDS-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^2 (range 10.0 to 241.1 mg/m^2).

The mean time to death was 177.9 days (range 1+ to 447+ days).

Study 30-38

Study 30-38 was a Phase IV prospective, randomized, double-blind, multicenter study comparing DOXIL with DaunoXome in the treatment of 80 patients with AIDS-KS. This post-marketing commitment study conducted between September 1996 and September 2000 was designed to satisfy the requirements of an Accelerated Approval. The study was not powered to demonstrate superiority of DOXIL over DaunoXome.

Enrollment was limited to patients with KS-associated symptoms that could be evaluated for clinical benefit. After two baseline visits to measure disease, patients with AIDS-KS of a severity requiring systemic chemotherapy were randomized in a 3:1 fashion to treatment with either DOXIL (20 mg/m^2 every 2 weeks) or DaunoXome (40 mg/m^2 every 2 weeks) for up to 6 cycles. At each study visit, patients were evaluated for clinical benefit (defined as an improvement in functional activity, pulmonary or gastrointestinal symptoms, KS-associated pain, self image and tumor response).

The presence of one or more of the following KS-associated manifestation was a prerequisite for eligibility for this study: 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 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%) and the median age was 38 years (range 23 to 75 years). Using ACTG staging criteria, 57% of patients were 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^3. Fifty-five percent of patients treated with DOXIL had received no prior therapy for AIDS-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 an 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, i.e. a sustained (at least 4 weeks) improvement from baseline in at least one of the five AIDS-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, with 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 ≥50% of previously raised lesions or area of indicator lesions decreasing by ≥50%, and response lasting at least 28 days. All tumor responses were partial responses, reported 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.

While clinical benefit was observed with both treatment arms, it was not possible to clearly delineate the degree of improvement that resulted from systemic chemotherapy and the degree of improvement due to antiretroviral therapy. Changes in antiretroviral therapy immediately prior to or during study, prior to scoring of clinical benefit, may have confounded the assessment of the effect of DOXIL on the AIDS-KS. The number of DOXIL patients (n=21) not confounded by changes in antiretroviral therapy prior to initiation of treatment with DOXIL was insufficient for the FDA to make a definitive conclusion regarding the clinical benefit of the patients treated with DOXIL. However in analyzing these 21 patients, there was a correlation with clinical benefit and response. Using the protocol definition of clinical benefit, all 8 of the 8 responders (100%) experienced clinical benefit, 8 of the 12 patients with stable disease (67%) experienced clinical

benefit and the one patient with progressive disease did not experience clinical benefit. The correlation is also present when applying the conservative definition of clinical benefit, as 5 of the 8 responders (62%) experienced clinical benefit, 5 of the 12 with stable disease (42%) experienced clinical benefit and the 1 patient with progressive disease did not experience clinical benefit.

REGULATORY HISTORY OF DOXIL IN KAPOSI'S SARCOMA INDICATION

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-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®*) 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.

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 were inadequate and did not provide substantial evidence of a clinical benefit for DOXIL in the treatment of AIDS-KS. FDA also communicated that antiretroviral therapy may be more effective treatment for AIDS-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 trial could have had an effect on the AIDS-KS, making assessment of the effect of DOXIL or DaunoXome on AIDS-KS difficult. The FDA requested that the Sponsor submit a new clinical study protocol and development plan to further assess the clinical benefit of DOXIL in AIDS-KS, and to satisfy full

approval of the AIDS-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 IV commitment. On 22 January 2003 the Sponsor received comments from FDA on the protocol design and discussions with FDA are ongoing to finalize the design of the phase IV commitment trial.

5. DESCRIPTION OF COMMITMENT STUDIES

5.1. Original Commitment Study: Sequus/Alza Study 30-38

Study 30-38 was designed as a prospective, double blind, randomized, multicenter trial. Study 30-38 enrolled 80 patients with AIDS-KS. Enrollment was limited to patients with KS-associated symptoms that could be assessed for potential clinical benefit from DOXIL treatment. Following two baseline visits to measure disease, patients were randomized in a 3:1 manner to treatment with either DOXIL (20 mg/m^2) or DaunoXome (40 mg/m^2) every 2 weeks for up to 6 cycles of treatment. At each study visit, patients were evaluated for clinical benefit defined as an improvement in functional activity, pulmonary or gastrointestinal symptoms, KS-associated pain, self-image and objective tumor response. Objective tumor response was reported as a Complete Response, Clinical Complete Response, Partial Response, Stable Disease, Progressive Disease, or Relapsed Disease.

Study results from this study were presented at the 2002 ASCO Annual Meeting.[16]

5.1.1. Summary of Study Sites

Eighty (80) patients were enrolled in 7 study sites throughout the United States.

5.1.2. Patient Population

Patients had to meet all of the following key criteria to be enrolled in the study:

1. AIDS-KS of a severity requiring systemic chemotherapy
2. One or more of the following symptoms:
   - KS-associated edema
   - Symptomatic evaluable pulmonary KS
   - Symptomatic evaluable gastrointestinal KS

- KS-associated pain
- KS lesions that are disfiguring or impair self-image

3. Five or more measurable mucocutaneous lesions

5.1.3. Endpoints

The primary efficacy endpoint was the proportion of patients who experienced clinical benefit as defined in the protocol.

Other planned efficacy endpoints were as follows:

- For each individual AIDS-KS symptom category, the proportion of patients who experienced clinical benefit based on an improvement from baseline
- Duration of clinical benefits
- The proportion of patients who experienced clinical benefit based on changes in medical interventions
- Response rate (proportion of patients who achieved a Complete or Partial response that lasted for ≥ 28 days)
- Duration of response
- Time to progression
- Survival

5.1.4. Efficacy and Safety Monitoring

5.1.4.1. Efficacy

The primary measures of efficacy were the proportion of patients experiencing clinical benefits and the duration of those benefits. Clinical benefit was defined as improvement in at least 1 of the following 5 symptom categories lasting for at least 4 weeks in the absence of disease progression or severe drug-induced toxicity:

Functional activity impaired by KS lymphedema

- Pulmonary symptoms (in patients with documented pulmonary KS)
- Gastrointestinal symptoms (in patients with documented gastrointestinal KS)
- Moderate-to-severe KS-associated pain despite analgesics
- Self-image altered by disfiguring KS lesions

Patients assessed the 5 symptom categories at each visit using an eleven-item questionnaire and rated the interference of symptoms with daily activities using a four-point scale. Additional efficacy parameters examined included:

- Tumor response (ACTG criteria)
- Changes in medical interventions used to treat the 5 symptom categories (i.e., diuretic or analgesic use for lymphedema, antiemetic use or RBC transfusions for gastrointestinal KS, etc.)
- Evaluation of photographs of patients by an independent reviewer blinded to patient treatment information

5.1.4.2. Safety

Safety of the study drugs was assessed by examination of adverse events and clinical laboratory assessments at each visit.

5.1.5. Statistical Design

This was a prospective, double blind, randomized, multicenter trial. The proportion of patients who experienced clinical benefit was estimated and the corresponding two-sided 95% confidence intervals of proportion were provided.

Duration of clinical benefit, duration of response, time to progression, and survival were estimated for each treatment group using the Kaplan-Meier method. Response rates of the two treatment groups were estimated. The corresponding two-sided 95% confidence intervals of response rate were provided.

The primary goal of this study was to describe the clinical benefits of DOXIL therapy in patients with Kaposi's sarcoma. The study was not designed or statistically powered to test for significant differences in clinical benefit or response rate between DOXIL and DaunoXome.

5.2. Proposed New Commitment Study

On 31 July 2002 the FDA sent a letter to the Sponsor that stated that the results of Study 30-38 did not provide substantial evidence of a clinical benefit for DOXIL in the treatment of AIDS- KS and requested a new phase IV commitment trail designed to demonstrate such clinical benefit in this patient population. On 27 November 2002, the Sponsor responded with a submission that included a proposed development plan, protocol outline and timeline to meet the phase IV commitment. The Sponsor has received comments from the FDA on this protocol design and discussions are ongoing with the FDA to finalize the design of the phase IV commitment trial.

6. DIFFICULTIES ENCOUNTERED IN CONDUCT, ACCRUAL OR COMPLETION OF TRIALS

6.1. Study 30-38

Changes in antiretroviral therapy immediately prior to or during the study confounded the FDA's ability to adequately assess the effect of DOXIL on AIDS-related Kaposi's sarcoma. As the widespread use of HAART did not begin until after Study 30-38 was initiated, the impact of HAART on subjects enrolled in 30-38 was not taken into account when designing the original study. As a result, the FDA felt that the data were insufficient to convert DOXIL from accelerated approval to full approval.

6.2. Proposed New Phase IV Commitment Trial

Difficulties that may be encountered with conducting any study in patients with AIDS-KS include the following:

6.2.1. Changes in Medical Practice

- **HAART utilization:** Patients who present with AIDS and KS are often treated with HAART and DOXIL concomitantly to achieve rapid cytoreduction, especially if the presenting AIDS-KS lesions are life-threatening, symptomatic or cosmetically disfiguring. Regression of AIDS-KS may occur 6-18 months after initiation of HAART as a consequence of viral suppression and immune reconstitution. In addition, the institution of HAART has resulted in reduction in the overall incidence of AIDS-KS.

- 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-KS agents will result in a significant reduction in the numbers of eligible AIDS-KS patients. Many patients with AIDS-KS who require systemic chemotherapy also may require modification of HAART for reasons of efficacy or safety, further complicating their eligibility for a pivotal trial or their continued participation in that trial.

- **DOXIL is the standard of care:** DOXIL is commercially available and is regarded as the standard of care for first- or second-line treatment of

AIDS-KS when systemic chemotherapy is appropriate. Currently 70% of patients with AIDS-KS are treated with DOXIL (IMS Health database).

6.2.2. Other Considerations

- **Incidence of AIDS-KS:** The widespread use of HAART has resulted in a markedly decreased incidence of AIDS-KS. It will be challenging to achieve enrollment targets with the low incidence of AIDS-KS in the United States.
- **Ethical considerations:** Ethical considerations and patient concerns/acceptance make it very difficult to conduct a placebo-controlled trial in this patient population. Delay of an active therapy of AIDS-KS is not an acceptable option to either patients or treating physicians. Furthermore, as DOXIL is regarded as the standard of care for patients with AIDS-KS for whom systemic chemotherapy is medically indicated, it may be equally as difficult to conduct a trial utilizing a "second choice" agent as a comparator.

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