3. Clinical Laboratory Data (Chemistry, Hematology, Urinalysis, etc.)

Except for the four patients terminated because of neutropenia and presented above, no patient discontinued study drug because of laboratory abnormalities. Three blood count components [absolute neutrophil count (ANC), hemoglobin, platelet count]; three liver function tests (alkaline phosphatase, SGOT, and total bilirubin) and one measurement of renal function (serum creatinine) have been selected as the most relevant indicators of potential study drug toxicity. The relationship between the measured value of the laboratory determination of interest and cumulative dose of DOXIL has been presented in the Integrated Summary of Safety. There is a slight down trend in (ANC) with increasing cumulative dose, but the decrease is small. The mean platelet count is quite steady up to 300 mg/m^2, an increase beyond that point may simply reflect the rather small number of patients. Hemoglobin as a representative measure of erythron was quite steady. The mean alkaline phosphatase measurements are relatively high throughout treatment but do not change significantly. The high value at 500 mg/m^2 represents a single patient. Values for SGOT tend to fall with continuing therapy as do values for bilirubin. The mean creatinine remains relatively constant.

With the possible exception of ANC these values are thought to be consistent with those that would be seen in a population of patients with AIDS-related KS not treated with DOXIL.

4. Clinical Literature Review

a. Data Base Search Strategy

An electronic database search, and a review of pertinent clinical publications appearing before [redacted], 19[redacted], identified a total of 29 articles and abstracts describing clinical experience with various formulations of liposomal doxorubicin.[135]

b. Summary of Published Safety Information for Liposomal Doxorubicin

In general, these publications describe early safety and pharmacokinetics trials, although a few present preliminary efficacy results. The following is a summary of conclusions derived from a review of the safety data presented in these publications.

The three studies on liposomal doxorubicin (L-DOX) reported by investigators supported by LTI refer to treatment of about 50 patients with solid cancers, including 35 with hepatic malignancies.[16,18-22] Across the three studies the doses and treatment courses administered varied; the lowest dose was 15 mg/m^2 i.v. dose in one pharmacokinetic study. In other studies L-DOX was administered either weekly, every 2 weeks, or every 3 weeks for between one and approximately seven courses. The AEs, which were observed at the higher doses (>50 mg/m^2), were myelosuppression, leukopenia, thrombocytopenia, agranulocytosis and depressed platelet count; immediate allergic reactions in 3 patients; mild transient pyrexia between six and 12 hours after injection, shivering and sweating; changes in hepatic enzymes; nausea and vomiting; sudden back pain during infusion; mucositis or buccal ulceration; mild alopecia; and red urine in one patient. Three of 24 patients in one Phase I clinical study died prior to completing their first full cycle of four treatments from gastro-esophageal bleeding, overwhelming malignancy, and pulmonary embolism following a deep vein thrombosis of the lower limb. Maximum tolerated doses, based on myelosuppression or confluent buccal ulceration in 2 or more patients, were determined to be 22.5 mg/m^2 for the weekly regimen and 70-100 mg/m^2 for the 3 weekly regimen.

LyphoMed Inc. supported research led to three reports on Phase I and Phase II clinical trials in patients with ovarian cancer, adenocarcinoma or breast cancer.[23-25] The 15 ovarian cancer patients received the liposomal preparation by intraperitoneal infusion over 1 hour, and then the fluid was drained 4 hours later.[23] These patients received doses between 20 and 100 mg/m^2; cycles were repeated every 21 to 28 days with patients receiving from one to eight treatments. The liposomal doxorubicin was administered by i.v infusion in the two other studies, with patients receiving doses of 30 to 90 mg/m^2 in treatment courses given every 3 to 4 weeks for two to twelve cycles.[24,25] The cumulative i.v. doses were from 120 to 885 mg/m^2. Patients in these studies experienced fever, nausea and vomiting (requiring hospitalization and rehydration for 2 patients); dose-dependent granulocytopenia at doses ≥ 60 mg/m^2, thrombocytopenia, leukocytopenia, reduced platelet count, normochromic, normocytic anemia; and hematological toxicity of grades 1 to 3; alopecia; lower back pain and chest pain during infusion; chills; and mild stomatitis. Eight of 12 patients in the Phase II study who received cumulative doses greater than 400 were assessed for cardiotoxicity; clinical congestive heart failure was reported for one patient but its relation to the study drug was uncertain. Another patient had a decrease in LVEF of 13% but no other clinical evidence of heart damage. A third patient with mild myofibrillar loss and dilatation of the sarcoplasmic reticulum involving less than 5% of myocytes was withdrawn from the study due to worsening cancer.

The Liposome Company supported studies report on the treatment of cancer patients (including adenocarcinoma, and squamous cell carcinoma) with TLC-D99 (and its precursor).[26-34] The patients received divided doses ranging from 20-37.5 mg/m^2 weekly for three consecutive weeks or doses of 20-135 mg/m^2, infused for 1 hour every 3 weeks. The adverse events included myelosuppression, leukopenia, neutropenia, thrombocytopenia, nausea and vomiting, alopecia, anorexia, mouth soreness, stomatitis, mucositis, fever, rigors, malaise, diaphoresis, flushing, chills, tachycardia, low back pain, nasal congestion, chest tightness, effects on hepatic enzymes, and cough. No effects were seen on cardiac function in one study. In another study no mention is made of development of symptoms of clinical cardiotoxicity, although two patients had a significant decrease in cardiac ejection fraction.

Three Japanese studies using different liposomal doxorubicin formulations in cancer patients have appeared.[35,36,135] AEs (fevers and leukopenia) were mentioned in only one of the abstracts for patients dosed with between 8 mg and 14 mg of liposomal doxorubicin.

c. Safety Conclusions Drawn from Studies with Liposomal Doxorubicin

Based on a review of safety information reported for all liposomal doxorubicin formulations administered intravenously at doses ranging from 10 mg/m^2 to 135 mg/m^2 as single and multiple treatment courses, adverse events are generally similar to those already reported for conventional Adriamycin.[70,74]

Myelosuppression and hematological changes, primarily in white cells, were the most serious events occurring at the higher doses. Stomatitis/mucositis was dose limiting for some patients. Hepatic changes occurred in a few patients but were not frequent, nor clinically significant in most cases. A few patients were reported to have reduced cardiac ejection fraction after liposomal doxorubicin, however, an insufficient number had received the high cumulative doses expected to provoke cardiac damage. With respect to potential cardiac toxicity, no attempt has been reported to systematically analyze the relationship between cumulative dose of liposomal doxorubicin and the incidence of cardiomyopathy. Dose-dependent alopecia was reported consistently. Nausea and vomiting occurred for some patients but could usually be controlled without antiemetics, although 2 patients needed hospitalization.

Low-grade fever and lumbar pain (on occasion of delayed onset) accompanied at times with chills and rigors, and malaise during the first 24 to 48 hours following treatment

appear to be adverse effects associated with liposomal doxorubicin administration. In the case of DOXIL administered to solid tumor patients as doses of 25 mg/m^2 or 50 mg/m^2, there appears to be a shift in the usual pattern of toxicity associated with a 3-weekly doxorubicin dosing schedule: neutropenia being the dose-limiting factor in a fewer number of cases and stomatitis/mucositis becoming dose limiting in more cases. Reversible hand-and-foot syndrome appears to be more frequently associated with multiple courses of DOXIL therapy than with conventional Adriamycin. The toxicity pattern seen with DOXIL resembles that seen with continuous infusion of unencapsulated doxorubicin.[99,101,136]

IX. DISCUSSION OF BENEFIT/RISK RELATIONSHIP AND PROPOSED POSTMARKETING STUDIES

A. Patient Population

It has been estimated that 10-18% of AIDS patients in the US develop Kaposi's sarcoma (KS).[137] Therefore, approximately 14,000-25,000 patients in this country are afflicted with this condition. In some of these patients the morbidity of progressive KS is substantial enough to warrant palliative treatment with systemic chemotherapy. Such patients generally present with advanced HIV disease, poor immune system status, and high tumor burden, and their KS is progressing rapidly on skin, mucous membranes, and in visceral sites. Visceral KS is contributing to a greater degree to overall mortality in the AIDS population as progress has been made in the treatment and prevention of *P. carinii* pneumonia (PCP) and other AIDS-related opportunistic infections.[138] Therapeutic options for advanced KS include single agent therapy with a vinca alkaloid such as vincristine or combination regimens such as vincristine with bleomycin (BV) or BV plus Adriamycin (ABV).

B. Clinical Indication and Patient Profile

Some patients' KS progresses despite standard chemotherapy, and other patients are unable to tolerate standard chemotherapy due to side effects of these agents and/or associated AIDS-related complications. No clearly proven treatment options exist for this population of patients. Therefore, approval is being sought for DOXIL under the proposed labeling of treatment for KS patients for whom standard multi-agent chemotherapy has failed.

In LTI Study 30-12, a cohort that included patients who had failed prior KS therapy was identified. Following review of individual patients' medical records, an expert panel of three AIDS KS clinical specialists agreed that 41/136 KS patients enrolled in this study had failed standard multiagent cytotoxic chemotherapy due either to disease progression (30 patients) or unacceptable toxicity (11 patients).

A typical patient in this treatment-failure category is a white (90.2%) 38-year-old (range 24-52) male (100%) homosexual (97.6%). Most (68.3%) have greater than 25 cutaneous KS lesions and 39% greater than 50. Almost half (43.9%) have oral lesions. Symptoms consistent with pulmonary and or intestinal KS were reported by 29.3% and 14.6% of patients, respectively. The majority are in a poor risk category for tumor burden (85.4%), systemic illness (61.0%) and immune system status (95.1%). The mean and median CD4+ lymphocyte count is 41.4 and 12 cells/mm^3, respectively. Despite the poor risk nature of this population, a mean Karnofsky performance status of 70.1 indicates that these patients can

care for themselves, carry on normal activity and do active work. The 41 patients in this treatment-failure group received a total of 299 doses of DOXIL therapy at a median per cycle dose of 20 mg/m^2 over a median of 146 days. The median cumulative dose for this group was 160.0 mg/m^2.

In the following discussion benefits accruing to patients receiving DOXIL therapy will focus on this treatment failure group. The discussion of risks will encompass larger patient groups (either all patients in Study 30-12 or 30-03, or, when appropriate, all patients in the NDA safety data base).

C. Clinical Benefit

In the setting of AIDS, KS effects the lives of patients in a variety of ways. Some of these are purely medical. Cutaneous lesions can become abraded and secondarily infected. Lesions of the oropharyngeal cavity can interfere with swallowing. In visceral disease lesions can impair pulmonary function and can lead to blood loss and abdominal pain. Edema of the extremities can reduce mobility.

KS can profoundly impact the quality of life and sense of well being of patients. At a very basic level, KS is a daily visible reminder to the patient that he is suffering from a fatal disease. Lesions can be painful and interfere with sleep. Raised lesions are noticeable and cosmetically unappealing when they occur on portions of the body not covered with clothing. Purple or red discoloration is ugly and unsightly. Genital lesions can detract from one's self image and interfere with sexual activity.

The clinical benefits followed among patients in the treatment failure cohort included flattening of previously raised lesions, lightening of color from purple or red to brown or more natural skin tones, loss of lesion associated nodularity and edema, and a decrease in pain. Flattening and color changes allow a patient more easily to cover lesions cosmetically. Decreasing edema alleviates discomfort, allows clothes and shoes to fit better, and prevents the breakdown of skin. A decrease in pain has obvious merit. The more of these benefits that occur the better. However very often a patient may experience only one benefit and still be clinically improved. Not infrequently benefits occur in sequence. Typically pain response and flattening precede color changes. Also, some clinical benefits may continue while others disappear. In addition, some patients experienced continued clinical benefit while the disease objectively progressed. For example, a patient could develop new lesions while subjectively more significant ones remain improved. Thus for that patient, despite evidence of progression, benefit is still maintained.

Based on measurable changes in lesion characteristics assessed in these 41 patients who were considered treatment failures, DOXIL therapy produced objective partial responses (PR) in the majority of patients, including 60% of those with disease progression and 82% of those who had experienced treatment-limiting toxicity (66% overall). The median duration of PR was 78 days. In this group, DOXIL treatment delayed disease progression for over 5 months with a median time to treatment failure of 162 days.

Table 49 presents quantifiable clinical benefits accruing to these patients. As shown, some patients experienced multiple clinical benefits associated with their tumor response.

TABLE 49
Clinical Benefits by Best Response

Best Response	N	Complete Flattening[a]	Color Improvement[b]	Pain Reduction[c]	Edema Reduction[d]
Partial	27	19	15	11	5
Stable	10	0	0	4	0
Progression	4	0	0	0	1
Total[e]	41	19/39 (49%)	15/37 (41%)	15/24 (63%)	6/10 (60%)

a) Number of patients whose previously raised indicator lesions were all flat for at least one cycle
b) Number of patients with red and/or purple indicator lesions at baseline with no red or purple indicator lesions for at least one cycle
c) Number of patients with moderate to severe KS-associated pain at baseline was reduced to mild or none for at least one cycle
d) Number of patients with edema at baseline that is absent from all indicator lesions for at least one cycle
e) Denominator represents # of patients with the potential for changes, i.e., moderate/severe pain at baseline; red/purple color at baseline; and raised lesion at baseline.

KS-associated pain was reduced in 15/24 (63%) of patients and most pain responders (11/15) achieved PR. This improvement in pain occurred at the time of the first PR in 10 patients, demonstrating that this clinical benefit is associated with response. The other four patients whose pain improved had stable disease. The use of concomitant analgesics did not account for the reduction in pain.

Tumor responses seen with DOXIL therapy were associated with important improvements in various aspects of the appearance of KS skin lesions in treated patients. These cosmetic benefits included flattening of previously raised lesions in 49%, change in color from a florid purple/red to a less noticeable brown in 41%, and reduction in lesion-associated edema in 60% of treated patients. All of these changes rendered the

lesions less obvious to the casual observer. The importance of these cosmetic benefits to persons with a highly visible, identifiable, and socially stigmatizing disease cannot be over-emphasized.

The importance of these benefits to patients is reflected in the results of a Quality of Life Questionnaire administered to those participating in Study 30-03. Scores for body image, KS status, pain, physical condition and functional ability were derived from an analysis of responses to questions. When the differences in scores at the time when patients' achieved their best tumor response and baseline were compared, statistically significant improvements were seen in all categories except functional ability.

D. Risks

A variety of toxicities occur in the setting of first line combination systemic chemotherapy in KS. Some of these can be medically severe in their own right such as severe neuropathy, myelotoxicity and pulmonary toxicity. These may exacerbate symptoms caused by the underlying HIV disease or other drugs. However some adverse effects of therapy could be acceptable if the therapy were curative, which in the case of KS it is not.

Minimizing the number of therapeutic agents used to treat KS minimizes the potential of known and undiscovered drug interactions. Some anti-HIV agents and drugs used as prophylaxis against opportunistic infections are myelotoxic (AZT, ganciclovir) or cause neuropathies (dDC, dDI). Each chemotherapeutic agent used to treat KS has the potential to exacerbate disease-drug interactions such as pulmonary dysfunction (bleomycin), neuropathies (vinca alkaloids) and myelotoxicity (Adriamycin, etoposide). The overall number of adverse events due to therapy can be minimized by decreasing the number of therapeutic agents employed. Thus if a single agent therapy such as DOXIL can serve as an efficacious alternative to combination therapies, an improvement in the treatment of disease is possible.

KS patients who received DOXIL therapy had advanced HIV disease, advanced KS and severely depressed CD4 lymphocyte counts. Clinical experience would suggest that when such patients are treated with standard cytotoxic chemotherapy, they are at risk for substantial toxicity. As described below, this was generally not the case with DOXIL therapy.

As expected, DOXIL-treated patients experienced leukopenia, an adverse reaction known to be associated with doxorubicin therapy. Among all KS patients in the NDA safety data base 254/435 (58.4%) experienced leukopenia possibly or probably related to DOXIL therapy.

About 15% of these patients experienced at least one episode of ANC < 500 cells/mm^3. Among all 30-12 patients, the minimum value for mean ANC was 1600, with 10% of patients (13/136) experiencing at least one episode of ANC < 500 cells/mm^3. Despite the frequency of neutropenia observed, bacterial or fungal septicemia attributable to DOXIL were uncommon across all studies (0.7%; 3/425) and only 4 patients discontinued DOXIL therapy due to neutropenia.

The relationship between DOXIL therapy and the incidence of new or worsening opportunistic infections is not known but cannot be discounted in light of the drug's myelotoxicity. Opportunistic infections (OIs) developed in a significant proportion of KS patients treated with DOXIL. In this respect, DOXIL recipients were similar to other cohorts of patients with advanced HIV disease treated with systemic chemotherapy for advanced AIDS-KS.[5,139] A review of adverse event listings indicated that 49/136 (36.0%) of patients in Study 30-12 experienced episodes of OIs. In Study 30-03, 131/244 (53.7%) of patients reported OIs. However, such infections were listed as the cause of temporary discontinuation of DOXIL therapy in only 15/793 (1.9%) of treatment courses in Study 30-12. The most frequently reported opportunistic pathogen was cytomegalovirus (CMV). CMV disease developed in 65/435 (14.9%) of patients and included infections of the CNS, gastrointestinal tract, lung and retina. The overall incidence of CMV among AIDS patients has steadily increased with the introduction of more effective therapy and prophylaxis for PCP.[140] The risk of developing CMV disease is particularly high among the KS patients included in this NDA due to the high proportion of patients with CD4 lymphocyte count < 100 cells/mm^3.[141] Other OIs reported among the 435 KS patients included candidiasis (20%), Herpes simplex (11.3%), PCP (7.6%), cryptococcosis (2.5%), mycobacterium avium complex (5.5%), toxoplasmosis (3.2%) and pulmonary aspergillosis (0.9%). It is difficult to ascribe a relationship between opportunistic infections in these patients to DOXIL therapy, given that most of the patients were already at extremely high risk for these infections due to their profound state of HIV-induced immunodeficiency.

Therapy with standard doxorubicin is associated with an increased incidence of congestive heart failure.[142] If the relationship between DOXIL dose and cardiomyopathy is similar to that of standard doxorubicin, the incidence of DOXIL-induced congestive heart failure would be about 2% at cumulative doses of 450 mg/m^2.[112] The recommended dose of DOXIL for AIDS-KS patients is relatively low (20 mg/m^2 every three weeks). Thus, to reach the cumulative dose range in which cardiotoxicity would become a significant concern (i.e., >450 mg/m^2) would require more than 20 courses of DOXIL therapy over 60 weeks. Therefore, for most patients being treated with DOXIL, at least 60 weeks will elapse before the cumulative dose reaches a range in which cardiotoxicity

will be of concern. It is noteworthy that preclinical studies in rats and dogs indicated that DOXIL is less cardiotoxic than standard doxorubicin.

Although the incidence of cardiac adverse events in patients receiving DOXIL was not unexpectedly high for an AIDS population,[126,130,133,143] no direct clinical evidence exists to support a claim that DOXIL therapy reduces this risk. The risk of developing DOXIL-related cardiomyopathy must therefore be assumed to be similar to that for standard doxorubicin.

Other common toxicities of standard doxorubicin therapy, such as alopecia, nausea and vomiting were relatively infrequent among the 435 KS patients treated with DOXIL (10%,15% and 6%, respectively). The lack of significant nausea/vomiting attributable to DOXIL therapy is beneficial to these patients who are generally cachectic as a result of their underlying HIV disease. The low incidence of alopecia is also beneficial to those patients who remain active, continue to work and interact socially.

Preclinical toxicologic studies have indicated that, compared with standard doxorubicin, DOXIL is less likely to produce tissue damage should the drug extravasate during infusion.

Two types of DOXIL-related adverse events may be related to the liposomal dosage form, an idiosyncratic acute reaction to the infusion and skin eruptions reminiscent of those seen with prolonged infusion of other chemotherapeutic agents. Acute reactions occurring during or soon after DOXIL infusion, characterized by sudden onset of facial flushing and in some cases shortness of breath, chest/back pressure/pain, and hypotension were experienced by 29/452 (6.4%) of patients in the NDA data base. In all cases the reaction occurred in the first cycle of treatment and recurred in only four patients during the second cycle. These reactions were self-limited and terminated within a few minutes of temporarily stopping the infusion or slowing the rate of infusion. Preclinical toxicologic studies noted similar reactions in dogs.

Skin eruptions probably related to DOXIL therapy were seen on the hands and feet of two solid tumor patients in study 30-02 after receiving multiple courses of DOXIL at 50 mg/m^2. In study 30-03, a total of 5/239 patients (2.1%) reported similar acral dermopathies. In study 30-12, one of the 136 treated patient reported a rash possibly related to DOXIL administration. If these skin eruptions are DOXIL-related, they seem to be dose-related. In no case did the reaction occur in the initial cycle of treatment. The condition cleared in 1 or 2 weeks off DOXIL. In preclinical testing, skin lesions developed in dogs and rats receiving multiple doses of DOXIL. A similar pattern of skin

toxicity has been reported for standard doxorubicin and other chemotherapeutic agents administered via prolonged infusions.[99]

E. Conclusions

Based on the considerations detailed above, warnings have been included in the DOXIL package insert to alert physicians of the potential for acute infusion-related reactions during the first few cycles of DOXIL therapy, skin eruptions, hematologic toxicity, and possible cardiac toxicity.

In considering the risks and benefits of alternative treatment for this patient population, it is clear that there are no anticipated benefits of alternative treatment because no clearly proven alternative treatment is available for patients in whom standard multi-agent systemic chemotherapy has failed. Treatment with α-interferon, an agent approved for treatment of KS, would not be expected to provide meaningful benefit to patients with advanced HIV disease and KS and CD4 lymphocyte counts < 100 cells/mm^3.[144] Alternate combinations of the chemotherapeutic agents proven effective for the treatment of AIDS-KS (doxorubicin, bleomycin, etoposide, vincristine, vinblastine) could be attempted. However, for patients such as those in the treatment failure cohort of Study 30-12, combinations including bleomycin and a vinca alkaloid with or without doxorubicin had already failed, leaving no useful alternatives.

For those in whom treatment failed due to toxicity, single- or multi-agent chemotherapy could be reintroduced after a recovery period. However, clinical experience suggests that KS would progress without chemotherapy and patients restarting the same or similar therapies would be at high risk for development of all the same toxicities that led to the initial discontinuation of therapy. With doxorubicin-containing regimens, these toxicities would include leukopenia, alopecia, nausea/vomiting, and cumulative dose-related cardiotoxicity. With the vinca alkaloids such as vincristine the development of drug-induced neuropathy at higher cumulative doses, or worsening of preexisting neuropathy caused by HIV disease or concomitant medications, is frequently dose-limiting. Possible bleomycin-induced pulmonary dysfunction and digital gangrene are cumulative dose-related risks facing patients who elect to restart conventional chemotherapy with that agent. In addition, many patients who are debilitated by HIV-related illness find that the acute toxicities of bleomycin (hyperpyrexia, rigors, profound fatigue) constitute a risk which is not balanced by the benefit obtained with this drug.

Given that these patients have advanced AIDS-KS, have failed standard cytotoxic chemotherapy and have no clearly proven treatment options, the benefits provided by DOXIL therapy outweigh the risks of DOXIL-related toxicity. Leukopenia is common

but manageable with the use of G-CSF. Fewer than 1% of KS patients treated with DOXIL (4/435) discontinued therapy due to neutropenia. The risk of developing DOXIL-induced cardiotoxicity in a KS population is relatively low because most patients do not receive a sufficiently high cumulative dose of drug during a typical course of therapy. Acute reactions to the infusion that occur in are self-limited, occur only during the first or second infusion and symptoms resolve quickly after stopping or slowing the infusion. Skin eruptions are rare and not dose-limiting. DOXIL-related alopecia, nausea and vomiting are relatively infrequent, so these toxicities, which are commonly associated with chemotherapy, would not be expected to significantly detract from the quality of life for these patients. DOXIL therapy stabilizes KS for a median of 5 months in patients who would almost surely progress without treatment. Partial responses are correlated with meaningful quantifiable clinical benefits including pain reduction, flattening and discoloring of lesions and resolution of lesion-associated edema. At the time of their best tumor response, KS patients believe that their quality of life has significantly improved in regard to KS disease status, pain and body image.

No postmarketing studies are being proposed at this time.