E. Safety Summary - General Safety Conclusions

The safety profile of DOXIL is derived from three sources. The first is the primary safety database, consisting of available data from five clinical trials; the majority of this section will be devoted to this database. The second consists of serious and/or unexpected AEs reported to LTI from other ongoing clinical trials and Named Patient Sales. The third is a review of the world wide clinical literature.

1. Primary Database

Four-hundred fifty-five unique patients, reflecting participation in four clinical trials are included in the primary safety databases (Table 43). Six patients participated in two trials. Overall, 256 patients participated in either European or Australian centers, 183 in U.S. centers, and 16 in Israel. Most of the patients, 440 of 455 (96.7%), were male, and most were white, 398 of 455 (87.5%). Twenty patients (4.4%) were Hispanic, 11 patients (2.4%) were Black, and 2 patients (0.4%) were Asian. Racial origin was either "other" or unknown for the remaining 24 patients. The mean age of all patients was 39.5 years, ranging from 16 to 73 years. Four hundred thirty-eight patients had AIDS-related KS and 16 patients had advanced malignancies.

TABLE 43
Enumeration of Patients Exposed to DOXIL in the Primary Safety Data Base

Study Number	Location	Planned Dose Range (mg/m^2)	Planned Cycle Frequency	Planned No. Cycles (range)	Number Exposed (N[a])
30-02	Israel	25 - 50	3 weeks	open	16[b]
30-03	Australia/Europe	10 - 40	2 weeks	open	247
30-05	U.S.	10 - 40	3 weeks	open[c]	18
30-12	U.S./Europe	20	3 weeks	open	131 (137)
30-14	U.S.	10 - 20	3 weeks	2	43
Total	--	10 - 40	2 - 3 weeks		455

[a] Unique number of patients enrolled (number of patients in study report; 6 patients were originally enrolled in other studies).
[b] One of the patients received only a single dose of Adriamycin and no DOXIL; all safety data from this patient is included nonetheless.
[c] Originally a two-period crossover study; indefinite extension treatment allowed by protocol amendment.

a. Extent of Exposure to DOXIL

A total of 455 patients in the primary safety data base received 3080 cycles of DOXIL. Of these, 6 patients initially enrolled in two studies (1 from Study 30-05 and 5 from Study 30-14) were transferred to Study 30-12; these patients are included only once in the overall total summary of dosing, and their entire dosing experience is linked together. Individual exposure to DOXIL varied by study and by patient. Dosing was to be administered in 2-week cycles for Study 30-03 and 3-week cycles for Studies 30-02, 30-12, and 30-14, but deviations were permitted for clinical reasons at the Investigators' discretion. Most commonly this was to permit recovery of the white count or because an intervening opportunistic infection needed priority treatment.

A summary of exposure to DOXIL, by cumulative dose and by number of cycles, is presented in Table 44. The wide ranges of cumulative doses in specific studies reflect the open-ended nature of all protocols except Study 30-03. Only 16 patients were exposed to doses larger than 350 mg/m^2. The total number of treatment cycles was 3080 cycles in 455 patients (6.8 cycles/patient), ranging from 67 cycles in the 43 patients enrolled in Study 30-14 (1.6 cycles/patient), to 2023 cycles in the 247 patients in Study 30-03 (8.2 cycles/patient). The overall mean dose of DOXIL per cycle was 18.6 mg/m^2 ± 6.27. The highest mean dose, 43.7 mg/m^2, was in the solid tumor study, Study 30-02, in which, after a 25 mg/m^2 trial in a few patients, the target dose was 50 mg/m^2. In the KS trials, the target dose early in the program was 10 to 40 mg/m^2 but later 20 mg/m^2 became the standard. The low doses in individual cycles represent infusions terminated because of acute infusion-related events.

TABLE 44
Summary of Exposure to DOXIL: Primary Safety Database

A: Enumeration of Patients Exposed to DOXIL by Cumulative Dose Range

	Cumulative Dose (mg/m^2)							
Study No.	≤50	51-100	101-150	151-250	251-350	351-450	451-550	Total[a]
30-02	2	3	5	3	2	0	1	16
30-03	50	61	31	71	20	10	4	247
30-05	5	5	4	3	0	0	1	18
30-12	21	45	31	35	5	0	0	137
30-14	43	0	0	0	0	0	0	43
TOTAL	**114**	**114**	**72**	**111**	**28**	**10**	**6**	**455**
(%)[a]	**(25.1)**	**(25.1)**	**(15.8)**	**(24.4)**	**(6.2)**	**(2.2)**	**(1.3)**	

B: Enumeration of Patients Exposed to DOXIL by Cycle

	No. of Cycles						
Study No.	1	2-4	5-10	11-20	21-30	31-50	Total
30-02	2	11	3	0	0	0	16
30-03	24	60	94	55	13	1	247
30-05	1	7	7	1	2	0	18
30-12	10	50	66	11	0	0	137
30-14	19	24	0	0	0	0	43
TOTAL (%)[a]	**55 (12.1)**	**145 (31.9)**	**172 (37.8)**	**66 (14.5)**	**16 (3.5)**	**1 (0.2)**	**455**

a One patient in Study 30-05 and 5 patients in Study 30-14 subsequently enrolled in Study 30-12 prior to the NDA data cut-off; the value in the total rows and columns reflect the actual number of patients and for this reason are not numerical tallies of the rows and columns.

Source: issjan[redacted]/t_dose2[redacted]v6.07 [redacted]:18:29

b. Adverse Events

1) Summary of All Adverse Events

AE data are available for 452 of the 455 patients in the primary safety database. Two patients in Study 30-03 and 1 patient in Study 30-12 had no AE forms available.

AEs are summarized in Table 45. They were frequently reported in this seriously ill population. Twenty-seven hundred seventy-seven AEs were recorded in the 3,080 cycles of treatment or just less than one AE per cycle. This pattern was maintained in the

individual studies; only Study 30-14 in which 121 AEs were reported in 67 cycles had a rate of more than one per cycle. It is evident, however, that if treatment continued long enough almost all patients would experience one or more AEs. Of the reported AEs, 19.5% were categorized as severe, 36.7% as moderate and 43.0% as mild.

Causal attribution is not readily established for most AEs because of the non-comparative nature of the trials, but the Investigators considered approximately one half of the AEs to be possibly or probably related to the study drug.

The level of attribution is further defined below. Eighty-three of the 2,777 AEs (3.0%) were considered related to study drug; this was indicated by a response of "definitely" in Study 30-02 (56.7%) and a response of "related" in Studies 30-03 (2.9%) and 30-05 (11.8%); there was no corresponding choice for Studies 30-12 or 30-14. A probable relationship was reported for 322 (11.6%) of the AEs; the percent of events with this response was similar for all five studies. The greatest number of AEs were thought to be possibly related to study drug, 921 events (33.2%), ranging from 14.3% in Study 30-12 to 41.0% for Study 30-03. Five hundred and fifty-four events (19.9%) were considered probably not or doubtfully related to DOXIL; these responses were not options in Studies 30-03 and 30-05. A total of 853 events (30.7%) were not related to study drug; this ranged from 0.0% in Study 30-02 to 47.1% in Study 30-05; "not related" was not used in Studies 30-12 and 30-14. In an additional 44 AEs (1.6%), the relationship between DOXIL and the AE was not specified.

TABLE 45
Summary of Adverse Events

	LTI 30-02	LTI 30-03	LTI 30-05	LTI 30-12	LTI 30-14	Total
Number of Patients	16	245	18	136	43	452
Number of Patients Reporting Adverse Events	12 (75.0%)	239 (97.6%)	18 (100.0%)	127 (93.4%)	32 (74.4%)	423 (93.6%)
Number of Adverse Events Reported	30	1906	85	638	121	2777
Severity of Adverse Events						
Severe	9 (30.0%)	374 (19.6%)	11 (12.9%)	147 (23.0%)	1 (0.8%)	542 (19.5%)
Moderate	10 (33.3%)	706 (37.0%)	28 (32.9%)	224 (35.1%)	52 (43.0%)	1019 (36.7%)
Mild	5 (16.7%)	814 (42.7%)	46 (54.1%)	264 (41.4%)	68 (56.2%)	1195 (43.0%)
Not Specified	6 (20.0%)	12 (0.6%)	0 (0.0%)	3 (0.5%)	0 (0.0%)	21 (0.8%)
Relationship of Adverse Events to Study Drug						
Definitely	17 (56.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	17 (0.6%)
Related	0 (0.0%)	56 (2.9%)	10 (11.8%)	0 (0.0%)	0 (0.0%)	66 (2.4%)
Probably	6 (20.0%)	227 (11.9%)	14 (16.5%)	55 (8.6%)	21 (17.4%)	322 (11.6%)
Possible	4 (13.3%)	781(41.0%)	13 (15.3%)	91 (14.3%)	32 (26.4%)	921 (33.2%)
Probably Not	3 (10.0%)	0 (0.0%)	0 (0.0%)	486 (76.2%)	67 (55.4%)	554 (19.9%)
Not Related	0 (0.0%)	813 (42.7%)	40 (47.1%)	0 (0.0%)	0 (0.0%)	853 (30.7%)
Not Specified	0 (0.0%)	29 (1.5%)	8 (9.4%)	6 (0.9%)	1 (0.8%)	44 (1.6%)

Notes: Within each patient, multiple adverse events which map to a single COSTART term are summarized as a single adverse event, to which the greatest severity and most probable relationship to study drug are assigned. Six patients in LTI 30-12 were originally enrolled in other studies. In the total column, these patients are included only once. "Definitely" relates was only used in LTI 30-02. "Related" was used in LTI 30-03 and LTI 30-05. "Probably Not" related was used in LTI 30-12 and LTI 30-14. "Doubtfully" and "Conditionally" were used only in LTI 30-02 and were mapped to "Probably Not" and "Possibly" respectively. "Not Related" was used in LTI 30-02, LTI 30-03, and LTI 30-05. All other relationship categories were used in all 5 studies.

Source: issjan[redacted]t_aesuma run by[redacted]on[redacted]:11:02

2) Summary of AEs Probably or Possibly Related to DOXIL in KS Patients

The remainder of this discussion will focus on AEs possibly or probably related to DOXIL in KS patients only since this is the population for which this drug is indicated. A summary of AEs possibly or probably related to DOXIL in KS patients by severity, body system and COSTART preferred term can be found in the Integrated Summary of Safety subsection in the Clinical Data Section of this NDA.

Of the 435 KS patients for whom AE data are recorded, 345 reported one or more AEs; one-third of the patients reported one or more events considered severe. Events referable to the body as a whole (fever, asthenia, headache, infection, in order of descending frequency), are all exceedingly common events in a population with advanced AIDS. Events referable to the cardiovascular system occurred in 33 patients (7.6%). It may be noted, however, that only two COSTART terms, vasodilation and hypotension were reported by more than 1% of the patients. Again, these are common findings in AIDS, particularly in the setting of wasting. Cardiovascular events of greater interest (cardiomyopathy, heart failure, arrhythmias, and the potential cardiotoxicity of DOXIL) are discussed in detail in subsection 8.

The most common AE referable to the gastrointestinal system was nausea, seen in 65 patients but reported as severe by only 3 patients. Other common digestive system AEs, in order of descending frequency were diarrhea, reported by 8.3% of patients, severe in 1.6%; oral moniliasis, seen in 6.9% of patients; stomatitis seen in 28 patients (6.4%); and vomiting, reported by 6.2% of patients. Stomatitis and the related COSTART term "mouth ulceration" are of interest in that they may well reflect doxorubicin toxicity. There were 28 patients with stomatitis and 9 with mouth ulcerations, of which, in total, only 4 were considered severe in intensity. Twenty-five were mild and eight of moderate intensity.

The organ system for which AEs were most frequently reported, by far, was the hemic and lymphatic system. Two hundred sixty-seven patients (61.4%) were noted to have AEs in this system. Leukopenia was most common occurring in 254 patients (58.4%). This reflects both lymphopenia and neutropenia, the former a hallmark of AIDS, the latter potentially a doxorubicin-related AE. Leukocyte findings are discussed further under laboratory evaluations. It should be noted that ganciclovir and trimethoprim-sulfamethoxazole are both bone marrow toxic, particularly for the granulocyte series. Anemia was very common (75 patients or 17.2%) but seldom severe (3 patients, 0.7%). Anemia is common in this population and is a documented adverse effect of AZT.

Thrombocytopenia was relatively less frequently observed, in 30 patients (6.9%) severe in 3. Only 4 patients had to discontinue the study drug because of bone marrow toxicity, in all cases due to neutropenia (see Section 7 below). The Investigators were able to manage the neutropenia with the use of colony stimulating factors (151 patients were treated with filgrastim and 14 with sargramostim), with delays in the schedule of DOXIL infusions and, less frequently, with reductions in dose. Anemia and thrombocytopenia were problems far more rarely.

AEs in the metabolic/nutritional disorder system were observed in 75 patients (17.2%). In descending order of frequency these were increased alkaline phosphatase, increased SGPT, weight loss, increased SGOT and hypocalcemia. Weight loss was considered mild or moderate in all cases and is a part of the AIDS syndrome.

Nervous system symptoms are common in AIDS and were reported in 33 patients (7.6%). Twenty-one different COSTART terms were recorded but emotional lability (1.8%), somnolence (1.6%), and dizziness (1.1%) were the only terms listed for more than 1% of patients. None of these reported events or frequencies can be differentiated from those regularly reported as part of the syndrome of AIDS.

Although respiratory findings were recorded in a total of 156 KS patients, in only 37 was the reported event thought to be possibly or probably related to investigational drug therapy. This is the biggest difference between total and probably/possibly related for any organ system. It may well reflect the Investigator bias that respiratory symptoms are most likely attributable to the opportunistic infections that are a feature of the underlying disease.

AEs referable to the skin and appendages were reported in 82 patients (18.9%). The most common, alopecia, was seen in 45 patients (10.3%). In only 6 patients was this considered more than mild. This incidence is probably less than would be seen with standard doxorubicin in similar doses. Herpes simplex was reported by 18 patients (4.1%) and rashes of various descriptions by 1% or less. Of particular note are the 7 patients in whom palmar-plantar skin eruptions occurred (see subsection 3., below)

Fourteen patients (3.2%) had findings referable to the special senses, the most common being retinitis. Cytomegalovirus (CMV) retinitis is a well known entity.

The only finding coded to the urogenital system in more than 1% of patients was albuminuria. This was seen in 20 patients (4.6%), and was mild in 16 and moderate in 4.

There were three unsual syndromes associated with administration of DOXIL, palmar-plantar erythrodysesthesia, stomatitis and acute reactions to the infusion. These are described in greater detail below.

3) Palmar-plantar Erythrodysesthesia

Seven patients developed palmar-plantar skin eruptions consistent with a mild erythrodysesthesia. Although acral dermopathies are not unusual when continuous infusions of cancer chemotherapeutic agents are administered, they are not common with standard bolus Adriamycin therapy. The occurrence of palmar and/or plantar skin eruptions in 7 patients is of concern because this syndrome appears to be a DOXIL-related AE not usually seen with conventional doxorubicin therapy. It was, however, reminiscent of the dermopathy associated with delivery of both doxorubicin and 5-fluorouracil by continuous infusion.[99,101,102,123]

Detailed case summaries of the seven patients with palmar-plantar erythrodysesthesia are presented in the separate report, Case Summaries of Safety.

Two solid tumor patients who received multiple cycles of DOXIL at 50 mg/m^2 in Study 30-02 developed desquamatory erythematous dermatitis of the palmar skin. One patient also experienced desquamation of the feet. Four KS patients participating in Study 30-03 who received greater than 6 cycles of DOXIL at 10 to 20 mg/m^2 developed exfoliative rash on the hands and /or feet reminiscent of anthracycline-induced palmar-plantar erythrodesthesia. One patient enrolled in Study 30-12 developed a mild rash on the arms and legs which was noted to worsen 1 week after each DOXIL infusion. Although the Investigator's opinion was that these symptoms were not related to DOXIL therapy, it is possible that they represent a mild palmar-plantar erythrodysesthesia.

If DOXIL-related, these events appear to be dose-related. In no case did it occur in the initial cycle of treatment, nor did it recur in any of the patients reported, whether or not subsequent cycles of treatment were at the same or a lower dose. The condition cleared in 1 or 2 weeks with or without treatment with corticosteroids.

Acral dermopathies, although not a very common cutaneous toxicity of chemotherapy, have led to a number of case reports in the dermatology, internal medicine and oncology literature under several synonyms: Burgdorf's syndrome, chemotherapy-induced acral erythema, hand-foot syndrome, palmar-plantar erythrodysesthesia, and toxic erythema of the palms and soles. Cytarabine, doxorubicin, and 5-fluorouracil are the most common chemotherapeutic agents associated with acral dermopathies, but the reaction has been

reported with a wide variety of agents. Most often the reaction is associated with continuous infusions of the chemotherapeutic agent,[99,101] and it is interesting to note that the pharmacokinetics of doxorubicin encapsulated in Stealth liposomes resemble, in some ways, those of a continuous infusion of doxorubicin. The dermopathy observed in the patients treated with DOXIL and reported above appears analogous to that which has led to the literature case reports. It is notable that repeat treatment was often possible without modification of dosage.

4) Stomatitis

Seventeen patients experienced moderate or severe stomatitis, that was considered drug-related, and was not due to candidiasis or any other obvious cause. Detailed case summaries of these 17 patients are presented in the separate report, Case Summaries of Safety.

5) Acute Infusion-related Toxicities

Twenty-nine patients suffered acute reactions to the infusion, 21 of them a consistent syndrome of flushing of the face and neck associated with chest tightness and occasionally with facial edema and dizziness. Four of the 15 patients treated with DOXIL in Study 30-02 developed an acute reaction, characterized in all cases by the sudden onset of facial flushing. This was associated with dyspnea in 3 patients and with weakness and a feeling of faintness in 1 patient. In no case were the symptoms severe; in all cases they were transient. Temporarily stopping the infusion or even slowing the rate of infusion allowed the reaction to terminate within a few minutes. In all 4 patients, the reaction occurred in the first cycle of DOXIL. In no patients were there symptoms in later cycles of treatment. Dyspnea was subjective; wheezing or other signs of bronchoconstriction were not reported. The only objective finding in these patients was facial flushing. No treatment was needed.

A similar syndrome occurred in 17 patients in the KS studies. In all instances the symptoms were noted in the first cycle of treatment, in two cases after only 2 or 3 minutes of the infusion, but after more drug had been delivered in others. Almost all patients complained of flushing of the face and neck and this was often observed by the Investigator. A feeling of dyspnea or chest tightness was common but objective wheezing was not reported. Facial and/or periorbital puffiness was common. Infusions were stopped and symptoms cleared in a few minutes to an hour or more regardless of whether any symptomatic treatment was used. Thirteen of these 17 patients received further cycles of DOXIL usually without any pretreatment or change in dose, and in only

4 did symptoms recur in the second cycle. In 1 of these 4, there was no recurrence in three later cycles at the same dose. The other 3 patients were not further treated. The higher incidence in Study 30-02 (median dose 50 mg/m^2/cycle) than in the KS studies (median dose 20 mg/m^2/cycle) suggests a possible dose relationship but none was apparent in the dose range used in the KS studies; and in one case the onset of the reaction came after only 1.6 mg/m^2 had been delivered.

The pattern of this idiosyncratic reaction makes it very unlikely to be allergic in origin. The reaction is self-limited and disappears with slowing or temporary discontinuation of the infusion, not recurring if the infusion is restarted. If the reaction does not occur on first exposure to DOXIL, it has not occurred in subsequent cycles.

An additional 8 patients in the KS study suffered a miscellany of acute infusion-related reactions not resembling the syndrome characterized above.

6) Deaths

In 161 of the 455 patients (35.4%) treated with DOXIL, death information was submitted to LTI. Of these deaths, 112 were reported as study termination reasons. The difference between the 161deaths and 112 patients for whom death is given as an early termination reason are accounted for by 49 patients terminated for other causes before their demise. Detailed case summaries of all deaths probably or possibly related to study drug, any death that occurred within one month of the last dose of DOXIL, and any death where the exact death date is unknown are presented in the separate report, Case Summaries of Safety.

As with study termination reasons, the cause of death categories are not unique and mutually exclusive, due to differences in the terminology used in the clinical trials. Fifty-two of the 161 deaths (32.3%) were attributed to intercurrent or non-AIDS related disease. Thirty-nine (24.2%) were attributed to progression of disease; 22 (13.7%) to disease-related complications; 7 (4.3%) to KS progression; 33 (20.5%) to non-KS AIDS-related complications; two of the deaths (1.2%) were classified as non-AIDS-related diseases; one of the deaths (0.6%) was a complication related to study drug; and 5 of the deaths (3.1%) had an unknown cause.

Twelve deaths (Patients 01-003, 01-005, 02-001, 02-004, 03-014, 06-027, 06-033, 08-007, 11-010, 14-007, 15-001, and 15-002), all in LTI 30-03, were considered to be probably or possibly related to study drug.

7) Discontinuations Due to AEs

Fifteen patients terminated study drug due to an adverse event, 12 in Study 30-03, 3 in Study 30-12. Six were terminated because they had acute infusion reactions. In 3 of them, the termination was after the first infusion. In 2 patients, a second infusion was attempted and when the AE recurred the study was terminated. These infusion reactions were not of different severity or character than those described above.

Four patients, all from Study 30-03, discontinued because of neutropenia. One patient was leukopenic and neutropenic at study entry and was on AZT, pentamidine and dapsone. He received 3 cycles of DOXIL, the first 2 at 20 mg/m^2, the third at 10 mg/m^2 but in spite of the dose reduction and the use of granulocyte colony-stimulating factor (GCSF), leukopenia and neutropenia persisted and the Investigator elected to discontinue therapy. He also had acute reactions to the infusions. A second patient developed a mild neutropenia after his sixth dose of DOXIL. The primary cause for terminating treatment however was failure to control the progression of his KS. On the 6th of October, he was hospitalized with bilateral pleural effusions and on the 12th of October he became jaundiced. This was diagnosed as obstructive jaundice due to post-hepatic portal obstruction with KS. The third patient had a marked drop in white count, neutrophils and lymphocytes after the initial cycle of treatment. He was poorly responsive to GCSF and treatment was discontinued. The fourth patient had a baseline white count of 2000/mm^3 and with only 500/mm^3 neutrophils. After his third dose of DOXIL, his total white count dropped below 1000/mm^3 and the Investigator felt it appropriate to discontinue investigational therapy.

Two patients developed cardiovascular AEs unrelated to DOXIL therapy. However, the Investigators considered that the potential cardiotoxicity of doxorubicin made it inappropriate to continue treatment. Finally, one patient received 1 dose of DOXIL 20 mg/m^2, on [redacted] 19[redacted]. "Unacceptable toxicity" is listed as the reason for discontinuation, but no toxicity is identified and no AE form was completed.
Two solid tumor patients (patients 1 and 4) participating in Study 30-02 discontinued DOXIL therapy due to progression of their underlying tumor.

8) Risk of Cardiotoxicity Associated with DOXIL

It is very difficult to define whether a particular intervention has resulted in cardiovascular toxicity in a population with AIDS and KS. Confounding presentations include dyspnea which is one of the most common symptoms in AIDS patients and is generally presumed to be of pulmonary origin because of the common occurrence of multiple opportunistic pulmonary infections. Dependent edema is common, particularly in patients with cutaneous KS lesions in the legs or KS lymphadenopathy; fluid accumulation in body cavities may be due to infection, tumor, or other non-cardiac cause.

When a diagnosis of cardiovascular dysfunction is established in KS patients, it is very difficult to characterize its cause. Cardiac involvement in AIDS was first reported in 1983 by Autran et al who noted myocardial KS at autopsy[124] and cardiovascular complications of AIDS have since been reported with increasing frequency - for a recent comprehensive review see Kaul et al.[125] In various series cardiomyopathy is reported in 10 to 42 percent (mean 23%) of AIDS patients[125] and accounts for approximately one-third of AIDS related cardiac deaths.[126] A prospective evaluation of an AIDS clinic population by two dimensional echocardiography[126] showed that 10 of 69 patients (14.5%) had global left ventricular hypokinesia; 11 additional patients from this cohort developed global LV dysfunction during a total of 725 months of follow up, for an incidence of 18% per year. Four of the 69 patients developed clinical congestive heart failure during the maximal 18 month follow up period. These authors calculated a crude prevalence rate of cardiomyopathy in AIDS patients approximately 300 times that of the general US population.

Major cardiac findings during postmortem examination are common, in 59 of 115 autopsies from the most extensive published experience, that from UCLA.[127] The most common finding in this series was serous pericardial effusion. Right ventricular hypertrophy was the next most common finding occurring in 18 cases and usually associated with the presence of interstitial pulmonary diseases. Respiratory failure was the principal cause of death in the majority of patients in the series as a whole. Kaposi's sarcoma involved the epicardium and myocardium in seven cases, in three the epicardium alone and in four extending to the myocardium. There were six cases of non-bacterial thrombotic endocarditis. No infective endocarditis was documented in this series although it has not been infrequently reported by others. Dilated cardiomyopathy was seen in two patients, an abscess in one and myocardial fungal infection in three patients. Although local interstitial cellular infiltrates are commonly seen (10% in Lewis's series[127]) the prevalence of myocarditis in autopsy series is difficult to establish with precision, in part because of a variable adherence to current histopathologic criteria. The

"Dallas" criteria for a diagnosis of myocarditis require myocyte damage or necrosis[128] and the usual observation is of non-specific infiltrates without documentable myocyte damage or necrosis. Kaul's review, however, reports a diagnosis of myocarditis in 184 of 402 AIDS autopsies (46%).[125]

There is no unanimity on the etiology of these cardiac findings, but it is known that HIV may infect the heart. Calabrese et al[129] were able to isolate and culture HIV from an endomyocardial biopsy specimen from an AIDS patient with congestive cardiomyopathy and Grody et al identified HIV by in situ hybridization in 6 of 22 patients who died of AIDS.[130] Drug induced cardiotoxicity is another possibility. Zidovudine clearly induces damage to the rat myocardium in a time and dose related manner.[131] This damage is characterized by wide spread mitochondrial swelling and disruption and is presumed to relate to the inhibition of mitochondrial DNA replication by the nucleoside. Similar mitochondrial abnormalities have been reported in biopsies obtained from patients with significant skeletal muscle myopathy associated with zidovudine therapy.[132] The development of cardiac dysfunction during therapy with zidovudine, ddI, or ddC, with improvement after its discontinuation, and the return of dysfunction with the resumption of therapy have all been reported.[133]

TABLE 46

Summary of Cardiovascular System Adverse Events by COSTART Preferred Term (KS Patients Only)

	Probably/Possibly	Total
Number of Patients	435	435
Number of Patients Reporting Cardiovascular Adverse Events	33 (7.6%)	69 (15.9%)
Cardiovascular System		
Angina Pectoris	0 (0.0%)	1 (0.2%)
Bundle Branch Block	1 (0.2%)	1 (0.2%)
Cardiomyopathy	2 (0.5%)	2 (0.5%)
Cardiovascular Disorder	2 (0.5%)	3 (0.7%)
Congestive Heart Failure	0 (0.0%)	2 (0.5%)
Deep Thrombophlebitis	1 (0.2%)	4 (0.9%)
Electrocardiogram Abnormal	0 (0.0%)	2 (0.5%)
Endocarditis	0 (0.0%)	1 (0.2%)
Heart Arrest	0 (0.0%)	4 (0.9%)
Heart Failure	2 (0.5%)	2 (0.5%)
Hemorrhage	1 (0.2%)	3 (0.7%)
Hypertension	0 (0.0%)	5 (1.1%)
Hypotension	5 (1.1%)	10 (2.3%)
Migraine	1 (0.2%)	1 (0.2%)
Palpitation	2 (0.5%)	2 (0.5%)
Pericardial Effusion	3 (0.7%)	5 (1.1%)
Pericarditis	0 (0.0%)	3 (0.7%)
Peripheral Vascular Disorder	1 (0.2%)	1 (0.2%)
Phlebitis	1 (0.2%)	3 (0.7%)
Postural Hypotension	0 (0.0%)	3 (0.7%)
Pulmonary Embolus	0 (0.0%)	3 (0.7%)
Shock	0 (0.0%)	1 (0.2%)
Syncope	2 (0.5%)	3 (0.7%)
Tachycardia	3 (0.7%)	8 (1.8%)
Thrombophlebitis	3 (0.7%)	3 (0.7%)
Thrombosis	1 (0.2%)	6 (1.4%)
Vasodialation	7 (1.6%)	7 (1.6%)
Ventricular Arrhythmia	1 (0.2%)	1 (0.2%)
Ventricular Extrasystoles	1 (0.2%)	1 (0.2%)
Ventricular Tachycardia	0 (0.0%)	1 (0.2%)

Note: At each level of summarization (global, body system, and COSTART preferred term), a patient is counted once if he/she reports one or more adverse events at that level. Six patients in LTI 30-12 were originally enrolled in other studies. In the total column, these patients are included only once.

Source: issjan[redacted]/t_aecardks run by [redacted] on [redacted] 12:22, revised [redacted] T-7CVA

a) Cardiovascular Adverse Events

Of the 435 patients in this NDA with AIDS-related KS, 69 (15.9%) incurred AEs referable to the cardiovascular system; in 33 patients (7.6%) the event was thought to be possibly or probably related to investigational drug therapy (Table 46). However, these listings include adverse events such as thrombophlebitis, migraine and vasodilation, which are not likely to be related to doxorubicin-induced cardiotoxicity. For 17 of these 33 patients the maximal intensity is listed as "mild." This incidence is comparable to that seen in the general population of AIDS patients not exposed to anthracyclines. Based on U.S. and European reports of HIV-related cardiac disease, Anderson and Virmani[134] found that 6 to 7% of HIV-infected patients had clinically significant cardiac disease.

The nature of events is also comparable to that reported in the literature. Pericardial effusions and/or pericarditis were reported in 8 patients. A precise cause was established in only 1 patient in whom malignant lymphoma was diagnosed and mycobacterial infections were thought to be responsible in 2. The etiology of the other effusions was unknown. As indicated above, pericardial effusion is the most common cardiac finding at autopsy in AIDS patients.[127] Arrhythmias were observed in 3 patients; in 2 there were ventricular extra-systoles, but in 1, ventricular tachycardia degenerating to ventricular fibrillation and requiring cardioversion. An additional 2 patients reported palpitations but no arrhythmia was documented. One patient had a mild conduction disturbance, incomplete right bundle branch block. There is little evidence that DOXIL was the cause of the cardiovascular problem in any of these patients, but as the patient profiles which follow indicate, contributing toxicity cannot always be excluded.

It must also be noted that the exposure of these patients to liposomal doxorubicin HCl was limited. The median cumulative dose was 100 mg/m^2 across all studies and only ten patients received more than 400 mg/m^2, a dose at which the cardiotoxicity of conventional doxorubicin HCl might begin to become manifest. At 100 mg/m^2 the expected rate of cardiomyopathy or congestive heart failure in HIV-positive patients treated with conventional doxorubicin would be less than 1%.

The CRF's of patients treated with DOXIL and recording COSTART diagnoses referring to the cardiovascular system were reviewed. This category includes many terms, e.g., thrombophlebitis, hemorrhage and migraine, not considered relevant to the evaluation of the potential cardiotoxicity of DOXIL. All patients with potentially relevant findings, whether or not they were attributed to investigational drug therapy are presented in the patient profiles which are presented in the Case Summaries of Safety in the Clinical Data Section of this NDA.

b) Cardiac Ejection Fraction

Forty-four patients, all from LTI 30-03, had a baseline cardiac ejection fraction measurement and at least one on-treatment measurement. In 37 of the 44 patients, the on-treatment ejection fraction measurements were normal, unchanged, or increased compared to baseline. In these 37 patients, the cumulative DOXIL dose at the time of measurement ranged from 20 to 460 mg/m^2.

In the seven remaining patients (Patients 01-006, 03-001, 06-007, 11-002, 11-003, 23-001, and 24-001), the on-treatment ejection fraction was lower than the baseline value. In these patients, the cumulative DOXIL dose at the time of measurement ranged from 30 to 500 mg/m^2. The lowest value reported for this group of patients was 18%, at a cumulative dose of 290 mg/m^2 (Patient 06-007). However, this measurement occurred during an episode of hypocalcemia, and a follow-up measurement, at a cumulative dose of 350 mg/m^2, reported an ejection fraction of 40%.

A complete listing of the serial ejection fraction results for all 44 patients is presented in the study report for LTI 30-03.

At the time of this NDA, the low cumulative exposure of DOXIL precludes a complete comparative assessment of the cardiotoxicity of DOXIL and conventional doxorubicin. However, the data available on all patients included in this NDA demonstrate that patients receiving DOXIL for a mean of 126.2 mg/m^2 do not have an increased risk of developing cardiac damage.

9) Opportunistic Infections

Adverse event reports were reviewed for evidence of opportunistic infections. Table 47 provides a summary of opportunistic infections, by study, for the KS patients. Of the 435 KS patients with adverse event data, 378 episodes of opportunistic infections were identified in 193 patients (44.4%). In decreasing frequency, the observed opportunistic infections were: candididasis (139 episodes in 87 patients), CMV (79 episodes in 65 patients), herpes simplex (62 episodes in 49 patients), PCP (35 episodes in 33 patients), MAC/MAI (28 episodes in 24 patients), toxoplasmosis (16 episodes in 14 patients), cryptococcal infections (12 episodes in 11 patients), aspergillosis (4 episodes in 4 patients), microsporidiosis (2 episodes in 2 patients), and one episode of an unspecified fungal pneumonia.

TABLE 47
Opportunistic Infections

	LTI 30-03	LTI30-05	LTI 30-12	LTI 30-14	TOTAL
Number of Patients	244	18	136	43	435
Aspergillosis	1 (0.4%) [1]	0	3 (2.2%) [3]	0	4 (0.9%) [4]
Candidiasis	66 (27.0%) [115]	0	14 (10.3%) [17]	7 (16.3%) [7]	87 (20.0%) [139]
CMV	38 (15.6%) [44]	2 (11.1%) [5]	22 (16.2%) [27]	3 (7.0%) [3]	65 (14.9%) [79]
CNS	0	0	2 (1.5%) [2]	0	2 (0.5%) [2]
GI	11 (4.5%) [13]	0	7 (5.1%) [9]	0	18 (4.1%) [22]
Pulmonary	3 (1.2%) [3]	0	3 (2.2%) [5]	0	8 (1.8%) [8]
Retinitis	20 (8.2%) [22]	2 (11.1%) [5]	9 (6.6%) [9]	3 (7.0%) [3]	34 (7.8%) [39]
Unspecified	6 (2.5%) [6]	0	2 (1.5%) [2]	0	8 (1.8%) [8]
Cryptococcal	6 (2.5%) [6]	0	5 (3.7%) [6]	0	11 (2.5%) [12]
Herpes Simplex	44 (18.0%) [57]	1 (5.6%) [1]	4 (2.9%) [4]	0	49 (11.3%) [62]
MAC/MAI	20 (8.2%) [23]	0	4 (2.9%) [5]	0	24 (5.5%) [28]
Microsporidiosis	2 (0.8%) [2]	0	0	0	2 (0.5%) [2]
PCP	24 (9.8%) [24]	0	9 (6.6%) [11]	0	33 (7.6%) [35]
Toxoplasmosis	10 (4.1%) [12]	0	4 (2.9%) [4]	0	14 (3.2%) [16]
Unspecified Fungal Pneumonia	1 (0.4%) [1]	0	0	0	1 (0.2%) [1]
TOTAL	131 (53.7%) [285]	3 (16.7%) [6]	49 (36.0%) [77]	10 (23.3%) [10]	193 (44.4%) [378]

Note: Entries indicate the number of patients with the opportunistic infection. Percentages are calculated using the total number of patients in the column. The number in brackets indicates the total number of occurrences of the opportunistic infection.

2. Secondary Safety Data Base

Between [redacted], 19[redacted], and [redacted], 19[redacted], 21 IND Safety Reports were submitted to the FDA. These safety reports involve a total of 21 patients who had received DOXIL. The reports for 11 of these patients reflect data already captured in study reports submitted in this NDA. Case report forms for the remaining 10 patients were not available at the time of data cut-off for this NDA. The safety reports for these 10 patients are summarized as part of the secondary safety data base.

There have been three safety reports to LTI through [redacted], 19[redacted], resulting from the named patient sales of DOXIL in Austria, Ireland, Israel, Italy and the United Kingdom. These three reports, involving 2 patients in Ireland, are included in the secondary safety data base.

Table 48 presents the clinical studies covered in this secondary safety database. The FDA Safety Reports are summarized in the Integrated Safety Summary.

TABLE 48
Enumeration of Patients Exposed (or to be Exposed) to DOXIL in Clinical Trials: Secondary Safety Database (Date: [redacted], 19[redacted])

Study Number	Location	Principal Investigator	Dose Range (mg/m^2)	Cycle Frequency	Number in Primary Safety Database	Number Exposed to date
AIDS-RELATED KS PATIENTS						
30-10	U.S./ Europe	(12 sites)	20	2 weeks	0	187
30-11	U.S.	(18 sites)	20	3 weeks	0	118
30-12	U.S./ Europe	(38 sites)	20	3 weeks	137	584
SOLID TUMOR STUDIES						
30-06-01	Israel	[redacted]	20 - 50	3 weeks	0	25[a]
30-06-02	U.S.	[redacted]	20 - 70	3 weeks	0	--
30-13	Israel	[redacted]	60 - 80	3 weeks	0	23
30-07	U.S.	[redacted]	60	3 weeks	0	17
30-18	U.S.	[redacted]	60	3 weeks	0	18
TOTAL	--	--	--	--	137	972

[a] Includes patients enrolled in Study 30-06-02.