C. Overview of Clinical Studies

Five clinical trials sponsored by LTI are included in this NDA. The three clinical pharmacology studies (Studies 30-02, 30-05 and 30-14) have been summarized in Section VIII.B above. The efficacy of DOXIL for its proposed indication is supported by two studies, Studies 30-03 and 30-12, which are described in Section VIII.D below.

Six publications have appeared in the scientific literature which report preliminary efficacy results with DOXIL 1. One paper, which focuses on the pharmacokinetics of DOXIL 1 in non-KS tumor patients,[43] describes two minor antitumor responses. These results are also presented in LTI Study Report 30-02 and a copy of the publication is included as an Appendix in that study report. The other five publications (one letter, two abstracts and two papers) describe interim results with DOXIL in the treatment of KS patients at individual study sites participating in LTI Studies 30-05,[44] and 30-03.[52-55] Copies of these are attached to the appropriate study reports. These publications are not discussed any further in this summary.

The safety of DOXIL, based on the 455 patients who have received DOXIL to date in all five studies, is summarized in Section VIII.E; a summary of the published literature describing non-DOXIL, liposomal doxorubicin is also included.

Based on interactions with the Division of Oncology and Pulmonary Drug Products of the FDA (the "Agency"), this NDA seeks approval for DOXIL in a limited indication, namely, treatment of AIDS patients with advanced KS which has failed standard first-line combination systemic chemotherapy due to disease progression or unacceptable toxicity. This patient population has no clearly established treatment options. The Agency provided guidance to LTI at four pre-NDA conferences ([redacted], 19[redacted]; [redacted], 19[redacted], [redacted], 19[redacted] and [redacted], 19[redacted]). The key points discussed at these meetings were the patient population being studied and the methods used to document antitumor response and clinical benefit.

- [redacted]
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In accordance with the Agency's recommendations, a cohort of 41 treatment failure patients has been identified among those enrolled in the primary efficacy study, Study 30-12. LTI's medical group screened case reports among 137 patients enrolled in this study and identified 65 patients who were potentially treatment failures. The section of the case report forms (CRFs) for each of these patients that documented prior therapy was sent to each of three expert panel members: Drs. [redacted], [redacted] and [redacted]. The panel members were not aware of the treatment outcome for these patients on DOXIL therapy. The panel members were instructed to select only patients who had received at least two courses of ABV or BV and who had, in their medical judgment, failed therapy. Based on unanimous vote, 41 patients were identified as treatment failures. This cohort has been analyzed for efficacy, with the primary analysis based on characteristics of five indicator lesions and a secondary analysis based on investigators' global assessment of whole body lesions. Clinical benefits including reduction in pain, resolution of indicator lesion-associated edema and nodularity and favorable color change were also followed. These methods are described in greater detail

in Section VIII.D.1. In response to the Agency's request, individual summaries have been prepared for each of these 41 patients based on information captured in CRFs and medical charts; the format has been discussed with the Agency. These can be found in the "Clinical Case Summaries for Refractory Patients" subsection of the Clinical Data Section of this NDA. Evidence presented elsewhere in this NDA and summarized below shows that such treatment failure patients derive meaningful clinical benefits from DOXIL therapy. As suggested by the Agency, this NDA also includes efficacy analysis of 238 patients enrolled in Study 30-03 as supportive evidence for DOXIL's antitumor activity.

D. Efficacy Studies Supporting the Indication

Two open-label, non-comparative, multinational efficacy trials (Study 30-12 and Study 30-03) have been conducted in patients with advanced AIDS-related KS (Table VIII.5). Both studies are currently ongoing.

TABLE 38
Overview of Clinical Studies Supporting the Indication

Study No.	Study Sites	N M/F[a]	Diagnosis	Mean Age (range)	Dose	Formulation
30-03	22 sites in Australia/ Europe	242/5	Kaposi's sarcoma	39.1 years (16 to 70 yrs)	10 - 40 mg/m^2 every 2 weeks	DOXIL 1 DOXIL
30-12	18 sites in US/Europe	137/0	Kaposi's sarcoma	38.3 years (24 to 68 yrs)	20 mg/m^2 every 3 weeks	DOXIL

[a] M=Male, F=Female

The primary clinical trial supporting the proposed indication is Study 30-12 which included a cohort of 41 patients retrospectively identified as treatment-refractory by three independent AIDS-KS clinical experts. This subgroup of 41 patients who failed prior aggressive chemotherapy was examined for evidence that DOXIL (administered as the proposed commercial formulation) provided an overall clinical benefit with reduction in tumor bulk and improvement in associated symptoms such as pain. Evidence that many of these high risk patients derived a clinical benefit from receiving DOXIL is summarized below. The clinical benefits achieved include a reduction in the bulk of the KS tumor, as well as an associated reduction in pain and improvement in the cosmetic appearance of the tumor. In addition, 96 patients who were not identified as treatment refractory were treated with DOXIL in Study 30-12 and evidence that many of these patients also attained clinical benefit is reviewed below.

Study 30-03 provides support for the efficacy demonstrated in Study 30-12. Clinical benefit is further demonstrated by the use of a structured quality of life assessment. These results indicate that DOXIL improves the quality of life of most KS patients while reducing tumor bulk. Study 30-03 was conducted using the previous formulations, DOXIL 1 and 2, and DOXIL.

1. Methodology: Measuring KS Response

The assessment of therapeutic efficacy of treatment for dermatologic cancers is difficult relative to the evaluation of treatment for solid tumors due to the inability to utilize advanced radiologic tools. Evaluation of patients with KS is further complicated since these patients may present with 100 or more individual lesions on the skin, a single large lesion may have several punctate satellite lesions associated with it, and a resolving lesion can break up into several discrete lesions. Some lesions, as they flatten, expand the area of residual pigmentation and hence, size of lesion is not necessarily reflective of healing (see, for example, the photographs presented in Figures 1-5, Summary of Risks and Benefits, Clinical Data Section of this NDA). Assessment of tumor extent and bulk therefore requires both rigorous clinical examination and clinical judgment.

Clinical judgment is an important component of response because the growth of a particular lesion may have important consequences if the lesion is on a visible portion of the clothed body or if a raised lesion occurs on a weight bearing surface or on an area of the body subjected to rubbing or other light trauma, such as on the belt line, on the collar line, or on the feet. Because the responses to therapy in KS and the ways in which KS adversely affect the lives of patients are multifactorial and complex, and inevitably involve some degree of judgment on the part of physicians and patients, a purely objective quantification of lack of therapeutic response ignores other clinical data that are important to patients.

In an effort to achieve an objective evaluation of response to therapy, up to five indicator lesions were chosen prior to DOXIL treatment, during the patients' initial evaluation. These five indicator lesions were to be assessed by the Investigators for size, thickness, color, nodularity and the presence or absence of edema or effusion. The changes in the five indicator lesion characteristics throughout treatment provide the basis of the primary efficacy analysis. The methodology used to assess indicator lesions is further described below.

The second assessment of tumor response incorporates Investigators' assessment of the patients' global condition and is intended to corroborate the primary efficacy analysis. Therefore, the Investigator assessment of response to therapy is used as a secondary indicator of efficacy, and is further described below.

An analysis of several indicators of clinical response and clinical benefit in Study 30-12 is presented in order to create a more complete picture of the efficacy of DOXIL. This analysis incorporates not only clinical response but the attainment of relief from pain and improvement of lesion color; the latter characteristic allowing for cosmetic manipulation which has particular importance in a disease which is socially stigmatizing. Clinical benefit is further described below.

a. Indicator Lesion Assessment

The primary efficacy analysis for LTI 30-12 is based on objective documentation of the five indicator lesions. At each visit the numbers of raised and of flat indicator lesions were recorded (along with other characteristics of these lesions). Thus, the percentage change in previously raised indicator lesions could be calculated.

The therapeutic response categories derived from this analysis include partial response (PR), stable disease (SD), or progressive disease (PD). A patient was coded as having achieved a PR at a given evaluation if there was a decrease of greater than or equal to 50% in the total size of the indicator lesions compared to study entry or a decrease of greater than or equal to 50% in the number of raised indicator lesions. A patient's response was coded at PD at a given evaluation if there was an increase of greater than or equal to 25% in the total size of the indicator lesions compared to baseline or any previous evaluation. Similarly, a patient's response was also coded as PD if there was an increase of greater than or equal to 25% in the number of raised lesions compared to baseline or any previous evaluation. Any increase in edema associated with any of the indicator lesions was coded as PD. In all other cases, response was coded as SD.

In LTI 30-03, five indicator lesions were also selected and followed prospectively. However, details of the raised or flat nature of the indicator lesions were not collected in a standardized fashion. Investigators were asked to describe the thickness of the lesion. These textual descriptions could not easily be translated to simply flat or raised. Hence, the indicator lesion assessment method has not been applied to the data in LTI 30-03.

b. Investigator Assessment

The primary efficacy analysis for study 30-03 and the secondary efficacy analysis for study 30-12 involved the investigator assessment of the patient's therapeutic response based on physical exam of the entire body. At each clinical evaluation, the protocol required investigators to assess response using five categories: complete response (CR), clinical complete response (CCR), partial response (PR), stable disease (SD), and progressive disease (PD). The reason for the response categorization was recorded by the investigator on a case report form. For example, if a patient achieved a PR, the investigator was asked to mark one of four boxes to indicate that the patient had no new lesions or new visceral sites of involvement, or the appearance or worsening of tumor-associated edema and at least one of the following:

(1) a 50% or greater decrease in the number of all previously existing lesions,
(2) complete flattening of at least 50% of all previously raised lesions,
(3) a 50% decrease in the sum of the products of the largest perpendicular diameter of the indicator lesions, or
(4) the patient met the criteria for clinical complete response except the patient has residual tumor-associated edema or effusion.

c. Clinical Benefit

In LTI 30-12, in order to assess the clinical benefits received by patients, analyses were performed on the changes in pain not associated with an increase in analgesic or anti-depressant medication, the disappearance of lesion-associated edema not associated with concurrent use of diuretics, improvement in lesion color, and flattening of lesions. The coincident improvement of these clinical criteria and the achievement of a partial response based on the indicator lesion assessment have been tabulated.

In LTI 30-03, the analysis of clinical benefit accrued during DOXIL therapy is presented as serial changes in quality of life as assessed by a questionnaire. This quality-of-life instrument is designed to generate results from five domains (or subscores): KS, pain, body image, physical condition, and functional ability. Changes in these subscores, from baseline to the time of the patient's best response to therapy, have been tabulated.

2. Efficacy Results

a. Patient Sample

Efficacy results obtained in the 438 KS patients enrolled in four protocols, Studies 30-03, 30-05, 30-12, and 30-14 serve as the basis for demonstration of DOXIL's antitumor activity. Patients in these trials were demographically similar (Table 39). The vast majority of the patients in these studies were homosexual (88.6%) and 2.3% were known drug users. This distribution is characteristic of AIDS-related KS.

KS status was staged according to the system proposed by ACTG which classifies extent of tumor, immune status and other AIDS-related disease manifestations, akin to the tumor-node-metastasis system used to stage other tumors.[122] Overall, immune status was poor, as defined by a CD4 count < 200 cells/mm^3, in 89.7% of patients. Forty-four percent of patients in the efficacy studies had presented with systemic symptoms or had a history of opportunistic infection. For refractory patients, the majority (56.1%) were poor risks for all three categories and only six of the refractory patients (14.6%) had a good tumor risk at baseline. Thirty-four (82.9%) of the refractory patients had poor tumor and immune system risk. The level of disability was reflected in an overall mean Karnofsky Performance Status score of 76.8%. Ninety-five percent had skin or subcutaneous lesions at baseline but 48.4% also had oral lesion, 22.8% pulmonary lesion and 12.6% had gastrointestinal disease.

The profound state of immune system suppression in these patients is reflected in their low CD4 lymphocyte counts. The mean and median CD4 lymphocyte counts were 183.3 and 30.5 cells/mm^3, respectively in Study 30-03 and 57.2 and 17.5 cells/mm^3, respectively in Study 30-12.

TABLE 39
Demographic Summary (KS Patients Only)

	LTI-30-03	LTI 30-05	LTI 30-12-REF	LTI-30-12-ALL	LTI 30-14	Total
Number of Patients	246	18	41	137	43	438
Sex						
Male	241 (98.0%)	18 (100.0%)	41 (100.0%)	137 (100.0%)	43 (100.0%)	433 (98.9%)
Female	5 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.1%)
Age						
Mean (SD)	39.0 (8.72)	38.6 (6.05)	38.4 (6.63)	38.3 (7.53)	39.0 (5.43)	38.8 (8.02)
Range	16 to 70	29 to 48	24 to 52	24 to 68	28 to 50	16 to 70
Race						
White	229 (93.1%)	13 (72.2%)	37 (90.2%)	121 (88.3%)	36 (83.7%)	397 (90.6%)
Black	7 (2.8%)	2 (11.1%)	0 (0.0%)	2 (1.5%)	1 (2.3%)	11 (2.5%)
Hispanic	5 (2.0%)	2 (11.1%)	2 (4.9%)	11 (8.0%)	5 (11.6%)	20 (4.6%)
Asian	1 (0.4%)	0 (0.0%)	1 (2.4%)	1 (0.7%)	0 (0.0%)	2 (0.5%)
Other/Unknown	4 (1.6%)	1 (5.6%)	1 (2.4%)	2 (1.5%)	1 (2.3%)	8 (1.8%)
AIDS Risk Factor[1]						
Homosexuality	210 (85.4%)	14 (77.8%)	40 (97.6%)	127 (92.7%)	42 (97.7%)	388 (88.6%)
Drug Abuse	10 (4.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (2.3%)
Other/Unknown	26 (10.6%)	4 (22.2%)	1 (2.4%)	10 (7.3%)	1 (2.3%)	40 (9.1%)

[1] Six patients in LTI 30-12 were originally enrolled in other studies. In the total column, these patients are included only once. Patients who indicated more than one risk factor (e.g., homosexual and IV drug user) are included in the Other/Unknown category.

Source: issjam[redacted]/t_demo_ies scv v6.07 [redacted]13:06

As expected, patients were receiving many concomitant medications. Two-thirds of the patients were taking one of the four available antiretroviral medications; AZT was the most frequently employed, in 178 patients, with dideoxyinosine (ddI), dideoxycytidine (ddC) and stavudine (d4T) in decreasing order. Eighty-four patients (20.3%) received more than one antiretroviral medication. Use of other antivirals was frequent: more than half the patients received acyclovir at some time during the trial, 23.1% ganciclovir and 12.4% foscarnet. Systemic antifungals were frequently employed with fluconazole being mentioned in 70.6% of the patients. Prophylactic therapy against opportunistic infections was the rule; sulfamethoxazole/ trimethoprim being the most used.

b. KS Response

Table 40 presents the data regarding best response achieved on study for Studies 30-12 and 30-03. These results are summarized below. Study 30-12 includes an analysis of the 41 patients who failed prior KS therapy and the total 136 patients included in the study. Study 30-03 response data are presented for 238 assessable patients of the 248 who were entered in the study. In addition, the primary and secondary efficacy analysis (indicator lesion assessment and Investigator assessment) are presented for Study 30-12.

1) Refractory Patients

Of the 41 patients who had progressive disease or toxicity on prior combination cytotoxic chemotherapy, 27 patients (65.9%) achieved a PR as their best response on study. In these same 41 patients, 10 (24.4%) achieved SD as their best response on study, while 4 patients (9.8%) achieved no more than PD as their best response on study. These numbers compared to a PR rate of 63.4%, a stable disease response of 31.7%, and a PD response of 4.9% when the Investigator assessment was analyzed.

Using the primary efficacy analysis, the refractory patients required a mean of 87.7 days (a median of 85 days) to achieve a PR. When analyzed by the secondary efficacy analysis, these times were similar with a mean time to PR of 97.1 days (median of 89 days).

The duration of PR is defined as the time between the evaluation when PR first occurs and the first subsequent evaluation when PR no longer occurs (typically because of progressive disease). As analyzed by the indicator lesion assessment, the 27 patients with PR maintained their response for a mean of 86.6 days (a median of 78 days). The 26 patients achieving a PR identified by the Investigator assessment maintained their response for a mean of 118.9 days (a median of 128 days).

TABLE 40
Best Response and Duration of Partial or Complete Responses

	30-12 Refractory Patients		30-12 All Patients		30-03 All Patients
	Investigator Assessment	Indicator Lesion Assessment	Investigator Assessment	Indicator Lesion Assessment	Investigator Assessment
Number of Patients	41	41	136	136	238
Best Response					
Complete	0	N/A	2 (1.5%)	N/A	15 (6.3%)
Partial	26 (63.4%)	27 (65.9%)	79 (58.1%)	84 (61.8%)	177 (74.4%)
Stable	13 (31.7%)	10 (24.4%)	40 (29.4%)	36 (26.5%)	44 (18.5%)
Progression	2 (4.9%)	4 (9.8%)	15 (11.0%)	16 (11.8%)	2 (0.8%)
95% Response CI[1]	(49%, 78%)	(51%, 80%)	(51%, 68%)	(54%, 70%)	(76%, 86%)
Time to PR and/or CR (Days)					
Mean (SE)	97.1 (10.10)	87.7 (9.66)	91.5 (5.66)	94.0 (6.25)	57.2 (4.43)
Median	89.0	85.0	84.0	85.0	33.0
Range	5 + to 198 +	1 + to 227 +	1 + to 198 +	1 + to 227 +	2 to 442 +
Duration of PR and/or CR					
Mean (SE)	118.9 (16.21)	86.6 (10.69)	119.5 (10.29)	82.0 (6.85)	117.2 (7.13)
Median	128.0	78.0	111.0	75.0	91.0
Range	1 + to 190 +	1 + to 150 +	1 + to 204	1 + to 169	1 + to 458 +

[1] 95% confidence interval for the proportion of responders (PR + CR).

Note: Mean, SE, and median are Kaplan-Meier estimates.
+ = censored observation (patient did not experience the event). If the largest observation is censored, then the mean value underestimates the true mean.

SOURCES: nda/t_tmdrallz run by [redacted] on [redacted] 11:37 nda/t_mdrrefz run by [redacted] on [redacted] 12:01 nda/t_prcrf run by [redacted] on [redacted] 14:21

Treatment failure is defined as PD after a patient experiences his/her best response. Using the primary efficacy analysis, 21 of 41 refractory patients (51.2%) experienced treatment failure at some point during therapy. The mean time to treatment failure (the period between start of therapy and PD) was 138.6 days (a median of 162 days) for the refractory patients. Using the secondary efficacy analysis (Investigator assessment), only 14 of 41 refractory patients (34.1%) are classified as experiencing treatment failure; the mean time to treatment failure was 172 days (a median of 218 days).

2) All Patients

When the 136/137 who were assessable for efficacy at the time of data base cut-off for Study 30-12 were analyzed by the primary efficacy analysis, 84 patients (61.8%) achieved a PR, 36 patients (26.5%) had SD, and 16 patients (11.8%) had PD as the best response on study (Table 40). Because the indicator lesion assessment method is not designed to identify a CR, no patients received a CR when the data were analyzed by this method. However, by the secondary efficacy analysis (Investigator assessment) 2 patients (1.5%) achieved a CR. Other results from the secondary efficacy analysis included 79 patients (58.1%) with a PR, 40 patients (29.4%) with SD and 15 patients (11.0%) with PD as their best response. Similarly, of the 238 patients in Study 30-03 assessable for efficacy, 15 patients (6.3%) achieved a CR, 177 patients (74.4%) achieved a PR, 44 patients (18.5%) achieved SD, and only 2 patients (0.8%) had PD as their best response.

The 136 patients in Study 30-12 needed a mean of 94 days (a median of 85 days) to achieve a PR by the primary efficacy analysis. Using the secondary efficacy analysis (Investigator assessment), these 136 patients needed a mean of 91.5 days (a median of 84 days) to achieve a PR or CR. The mean duration of the PR was 82 days and the median 75 days when analyzed by the primary efficacy analysis. This duration changes to a mean of 119.5 days and a median of 111 days when analyzed by the secondary efficacy analysis.

The time to achieve a PR or CR was shorter for the 238 patients in Study 30-03. The mean time to achieve a PR was only 57.2 days (a median of 33 days). While the time to achieve a PR or CR in Study 30-03 was shorter than the time needed in Study 30-12, the duration of the partial or complete responses is very similar. The response of patients who achieved a PR or CR persisted for a mean of 117.2 days (a median of 91 days).

Seventy-one of 136 patients (52.2%) with efficacy data in Study 30-12 were found to have treatment failure when analyzed by the primary efficacy analysis. Using the

secondary efficacy analysis, 46 of 136 patients (33.8%) were found to have treatment failure. Mean time to treatment failure was 129 days (a median of 135 days) using the indicator lesion assessment method and was 165.6 days (a median of 189 days) using the secondary efficacy analysis. For Study 30-03, 73 of 238 patients (30.7%) experienced treatment failure. The mean time to treatment failure was 275.7 days (a median of 250 days).

c. Clinical Benefits Accruing to Refractory Patients

In addition to the objective tumor responses achieved, as measured by the primary and secondary efficacy analyses, a significant percentage of the 41 patients who had failed prior therapy experienced measurable clinical benefits while being treated with DOXIL; clinical benefit in these patients is summarized by best response category in Table 41. The proportion of patients experiencing clinical benefit were enumerated for pain reduction, color improvement, lesion flattening, and edema reduction. The following criteria were used for clinical benefit: (1) pain reduction in a patient with moderate to severe KS-associated pain at baseline occurred when pain was reduced to mild or none for at least one cycle during therapy; (2) color improvement occurred in a patient with red and/or purple indicator lesions at baseline, who subsequently had no red or purple indicator lesions for at least one cycle while on therapy; (3) in a patient who had at least one raised lesion at baseline complete flattening occurred when all indicator lesions were all flat, for at least one cycle while on therapy; (4) edema reduction occurred in a patient with edema at baseline, when edema was absent from all indicator lesions for at least one cycle while on therapy. The denominator for calculating the percentage varies from category to category because a variable number of the 41 patients qualified for consideration for these assessments of clinical benefit.

TABLE 41
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., edema at baseline, moderate/severe pain at baseline; red/purple color at baseline; and raised lesion at baseline.

Overall, 15 of the 24 treatment refractory patients (63%) who reported moderate/severe pain at baseline achieved pain reduction while on DOXIL therapy. A total of 11 patients, who achieved a PR by the primary efficacy analysis, experienced a pain reduction while on therapy. An additional 4 patients, who achieved SD as their best response on therapy, also achieved pain reduction. A total of 37 of the 41 patients presented with red and/or purple indicator lesions at baseline, and a total of 15 patients (41%) had no red or purple indicator lesions for at least one cycle while on DOXIL therapy. In addition, 19 patients achieved complete flattening of all indicator lesions for at least one cycle while on therapy. These 19 patients represent 49% of the 39 eligible patients. All 19 of these patients also achieved a PR during the course of the study. Finally, a total of 6 out of 10 eligible patients experienced a reduction in KS lesion edema at any point throughout the course of the study.

Pain reduction in the 15 refractory patients who experienced it lasted for an estimated median of more than 241 days. Color improvement, which typically starts later in the course of therapy, in the 15 refractory patients who experienced it, lasted for a median of 86 days. Complete flattening in the 19 refractory patients who experienced it lasted for an estimated median of more than 190 days

Of the 41 treatment refractory patients, 6 patients achieved a clinical benefit in three of the four categories at any time throughout the study and all 6 of these patients are listed as having achieved PR. Nine patients achieved a clinical benefit in two of the four categories, while 15 patients achieved a clinical benefit in one of the four categories. Finally, 10 patients failed to achieve a clinical benefit in any of the four categories. These 10 patients contained 3 of the 4 patients with PD, and only 1 PR patient. One patient achieved clinical benefit in all four categories at some point during therapy. This patient's best objective response was PR after seven cycles. Therefore, there was a high degree of association between the response determined by our primary efficacy analysis and the clinical benefits achieved for these patients.

More detailed individual patient summaries that chronicle these and other clinical benefits accruing to these refractory patients are presented in Clinical Case Summaries for Refractory Patients in the Clinical Data Section of this NDA.

d. Quality of Life Questionnaire

Study 30-03 incorporated a quality of life questionnaire which included five domains. These domains were functional ability, pain, KS-specific questions, body image, and physical condition. Improvements in quality of life were expressed as positive values, lessening quality of life as negative values. The mean total score and scores for the five domains at baseline and the time at which the patient achieved his/her best KS response were compared (students' paired t-test) and the results are presented in Table 42. A statistically significant improvement occurred in pain ($p = 0.0220$), KS-specific questions ($p = 0.0001$), body image ($p = 0.0001$), physical condition ($p = 0.0074$), and total score ($p = 0.0001$). No statistically significant improvement occurred in functional ability.

TABLE 42
Quality of Life Comparisons from Study 30-03

	Baseline Score	At Best KS Response
Total Score	-0.5	6.2 ($p = 0.0001$)
KS	-1.8	1.2 ($p = 0.0001$)
Pain	0.2	0.5 ($p = 0.0220$)
Body Image	-4.0	-3.4 ($p = 0.0001$)
Physical Condition	1.7	3.1 ($p = 0.0074$)
Functional Ability	4.1	4.7 ($p = 0.1476$)

3. Discussion of Results from Efficacy Trials

These data provide support for the intended claim that DOXIL treatment produces objective clinical responses, as well as clinical benefit to and improvements in the quality of life of patients with AIDS-related KS, including those who have failed prior systemic combination chemotherapy due to progressive disease or intolerant toxicity. Data to support this indication are derived from 41 patients who had failed prior chemotherapy and were treated with DOXIL in Study 30-12. Twenty-seven of the 41 patients achieved a PR as determined by objective measurements of their cutaneous lesions. Sixteen of the 27 patients experienced improvement in at least two of four identified areas of clinical benefit. Taken together, these results demonstrate that DOXIL therapy of patients with AIDS-related KS who have exhausted all prior therapies results in meaningful clinical improvements.

A high proportion of the total patient population in both efficacy studies (Study 30-03 and Study 30-12) achieved a PR or CR. These response rates compare favorably with the published response rates for treatment with combination cytotoxic chemotherapy consisting of Adriamycin, bleomycin, and vincristine. One open label randomized study of advanced stage AIDS KS patients comparing ABV with single agent Adriamycin at a dose of 20 mg/m^2 given every two weeks, reported an overall partial plus complete response rate of 88% for ABV and 48% for Adriamycin.[5] Single agent doxorubicin administered weekly at a dose of 15 mg/m^2 was reported to yield a 10% partial response rate in KS patients.[4] Overall, the results obtained in Studies 30-03 and 30-12 for all patients combined compare favorably to the results published in the literature for treatment of KS with combination cytotoxic chemotherapy. The response rates achieved with DOXIL are considerably higher than that achieved with single agent doxorubicin. Therefore, DOXIL appears to be as effective as combination cytotoxic chemotherapy and more effective than single agent doxorubicin in the treatment of KS.

This conclusion is supported by an analysis of a subgroup of patients in Study 30-12 who entered the study due to disease progression and who had received prior Adriamycin therapy. These patients received Adriamycin in combination with a vinca-alkaloid and had progressive disease, but once treated with DOXIL, 10 of 20 (50%) patients achieved a partial response on DOXIL. Eight of 20 patients (40%) achieved a stable disease response while 2 of 20 patients (10%) achieved progressive disease as the best response on DOXIL therapy. Therefore, half of patients who received doxorubicin as part of chemotherapy and had progressive KS prior to DOXIL therapy subsequently responded. This indicates that doxorubicin delivered in the Stealth liposome improves the antineoplastic activity of the anthracycline.

The PR achieved by 27 of the 41 patients who failed prior chemotherapy continued for a median duration of 78 days. Considering the advanced stage of AIDS in this patient population, a two and one-half month duration represents a considerable proportion of the expected survival for these patients. In addition, for many patients the clinical benefits achieved from DOXIL therapy persisted for quite some time after the objective response ended. The clinical benefits persisting after the end of the objective response include continued reduction in KS lesion-associated pain and persistence in the color improvement. Therefore, while the objective response lasted approximately two and one-half months, the clinical benefit persisted.

KS affects the lives of AIDS patients in a variety of ways. Medically, cutaneous lesions can become abraded and secondarily infected. Dermal lesions also cause a deterioration in the quality of life, self-image, and sense of well-being of patients. Lesions in the oral-pharyngeal cavity can interfere with swallowing. KS is a daily, visible reminder to the patient the he or she is suffering from a fatal disease. Clinical benefits derived from DOXIL therapy included a reduction in pain associated with KS lesions, improvement in the color of the KS lesions, a complete flattening of all indicator lesions, and disappearance of any KS lesion-associated edema. A reduction in KS lesion-associated pain can be easily translated into an improvement in the quality of life of the patient. The improvements in pain were accomplished in the absence of any discernible increase in concomitant pain medication. Improvements in KS lesion-associated color translate into improvements in the patient quality of life as the patient is able to cosmetically hide unsightly lesions and, therefore, minimize the negative social impact of this stigmatizing disease. Flat lesions are also more amenable to cosmetic camouflage. In addition, flattening of lesions on the belt line or feet lessens the chance of abrasion and consequent infection. 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 others remain improved. Thus for that patient, despite evidence of progression, benefit is still maintained

4. Efficacy Conclusions

Treatment with DOXIL is efficacious and provides a reasonable tumor response and a clear and meaningful clinical benefit, in the treatment of patients with AIDS-related KS who have failed or are intolerant to conventional combination chemotherapy. The primary analysis of efficacy based on assessment of indicator lesions and the secondary analysis based on investigator assessment provide nearly identical results. Documented

clinical benefits include flattening of all indicator lesions, improvement in the color of indicator lesions from purple or red to a brown or more neutral color, a reduction in KS-associated pain and a reduction in KS lesions-associated edema and nodularity.

DOXIL used in the treatment of the broader population of KS patients was also seen to be efficacious. Results from all patients treated in Studies 30-03 and 30-12 were consistent with those achieved in the refractory patient subset.

As demonstrated in Study 30-05, there was a prolonged doxorubicin plasma circulation time after the administration of DOXIL relative to the administration of Adriamycin. This long circulation time was associated with higher doxorubicin concentrations in KS lesions of patients who received DOXIL. These concentrations exceed those found in normal skin as demonstrated in Study 30-14.

Taken together, these four clinical trials establish that doxorubicin encapsulated in long-circulating liposomes remains circulating in the blood stream for extended periods of time, allowing for accumulation of doxorubicin in KS lesions which translates into a reduced tumor bulk and clinical benefit for a population of patients with no other therapeutic options.

Clinical Study Reports Referenced

Report Number:	LTI-30-03
Report Title:	DOXIL (Stealth® Liposomal Doxorubicin HCl) Injection in the Treatment of AIDS-Related Kaposi's Sarcoma: A Phase 2/3 Clinical Study Interim Clinical and Statistical Report
Study Dates:	[redacted], 19[redacted] - [redacted] (NDA data cut off date: [redacted], 19[redacted])
Report Date:	[redacted] 19[redacted]
Principal Investigator:	Multicenter (see study report for list of investigators)
Study Site:	Multicenter (see study report for list of study sites)

Report Number:	LTI-30-12
Report Title:	Open Trial of DOXIL® (Stealth® Liposomal Doxorubicin HCl) Injection in the Treatment of Moderate to Severe AIDS-related Kaposi's Sarcoma
Study Dates:	[redacted], 19[redacted] - [redacted] (NDA data cut off date: [redacted], 19[redacted])
Report Date:	[redacted], 19[redacted]
Principal Investigator:	Multicenter (see study report for list of investigators)
Study Site:	Multicenter (see study report for list of study sites)