

Table 19. FDA Analysis of Patients who Responded to Uvadex with Photographic Evidence of Improvement in Several Clinical Benefit Parameters, (CTCL 3)

Patient No.	Improvement in Scaling	Decrease in Edema	Decrease/Resolution of Erythema	Disappearance of Lesions
	X	X	X	
	X	X	X	
				X
			X	
			X	X
		X	X	
		X	X	
		X		
	X			
		X		
		X		
			X	
			X	

Sponsor's Analysis of Duration of Tumor Response

Duration of response was calculated as the number of days a $\geq 25\%$ decrease from baseline was maintained. The median duration of response was 140 days for the patients who responded within six months and in the intent to treat group in CTCL 3 compared to 419 and 173.5 days for the two oral methoxalen studies (CTCL 1 and CTCL 2, respectively).

Reviewer's comment: The longer duration of response in CTCL 1 is probably due to the longer length of follow-up and less drop-outs compared to study CTCL 2 and CTCL 3.

Sponsor's Analysis of Survival

Deaths from all causes and patients lost to follow-up were considered in the analysis. The last known date alive was used where death date was not known or not applicable. Median survival for patients in CTCL 1 is 126.9 months from the date of diagnosis and 65 months from the date of first treatment. The survival analysis of 20 patients with lymph node biopsy positive disease was 47 months from the date of first treatment.

Reviewer's comment:

Primary survival data on CTCL 1 was not available in this NDA submission. The survival curve calculations were done after 19 of the 39 patients (49%) died. For the rest of the patients (51%), survival date was censored for the last known date to be alive. (NDA 20,969 vol.14, p.135).

The overall median survival from diagnosis reported in the literature for patients with CTCL is 42 months while the survival of patients with lymph node involvement is 34 months.¹² It appears that survival is improved with 8-MOP regardless of disease stage. However, caution must be observed regarding possible lead time bias. Since publication of this reference article in 1983, there have been numerous advances in the treatment and support of patients with CTCL, such as chemotherapy/biotherapy combinations, better and stronger antibiotics for the treatment of opportunistic infections, etc.

Table 20. Median Survival Following Methoxalen Treatment (CTCL1,3)

Study	Median Survival (Months)			
	From Date of Diagnosis		From Date of First Treatment	
	Sponsor's Analysis	FDA Analysis	Sponsor's Analysis	FDA Analysis
CTCL 3	125	122.6	Indeterminate	Indeterminate
CTCL 1	127		65	

¹² Winkler CF. Cutaneous T-cell Lymphoma: a review. CRC Critical Reviews in Oncology/Hematology, 1983; 1(1):49-92.

Reviewer's comment: *Survival analysis of CTCL 3*

Survival was not an endpoint of CTCL 3. The median survival from the date of diagnosis appears to be 122.6 months (sponsor's, 125 months) and the median survival from the first day of treatment cannot be determined.

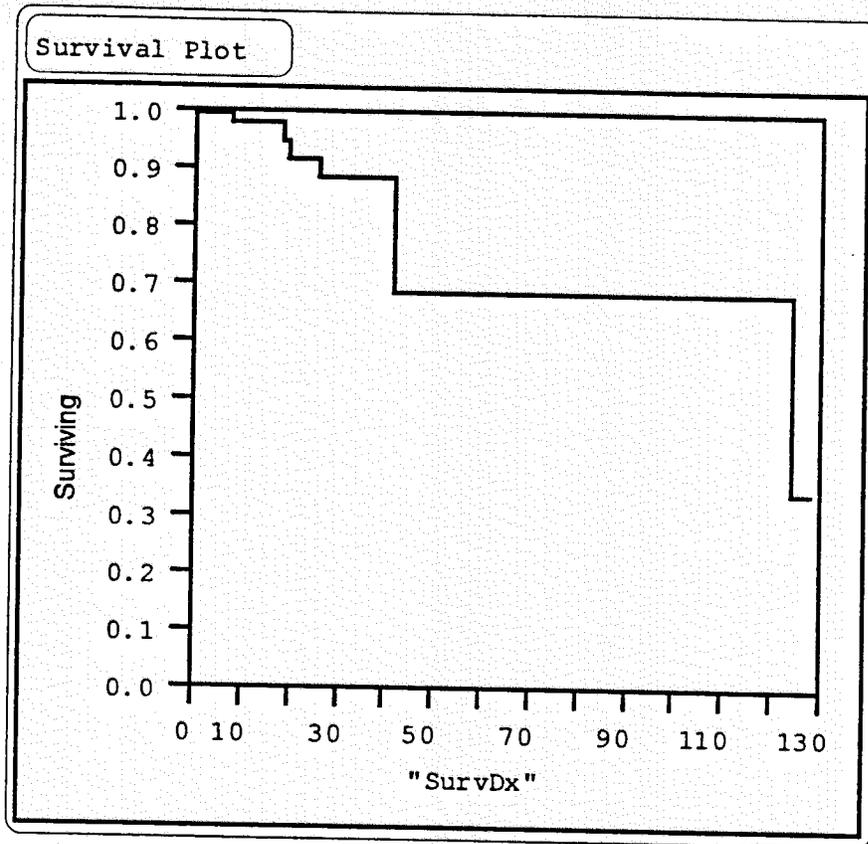
This data should be interpreted with caution since there was overcensoring of patients for survival. There were only seven out of 51 patients who died and 44 patients censored either on the last day of treatment, last day of follow-up or last day known alive. The survival profile on the seven patients is as follows:

Table 21. Survival Data on Uncensored Patients (CTCL 3) (months)

Patient	From Date of First Treatment	From Date of Diagnosis
	1.01	7.92
	9.3	18.91
	16.6	124.7
	19.4	19.3
	25.75	26.25
	29.93	42.03
	34.9	42.1

Note that since patient 3 was treated with Uvadex much later after diagnosis, his survival duration was 124.7 months despite being on study for only 16.6 months. This spuriously prolonged the overall median survival from the date of diagnosis for the whole group since there were only seven recorded deaths and the rest were censored. The following graph was created from JMP to illustrate the survival curve from the date of diagnosis:

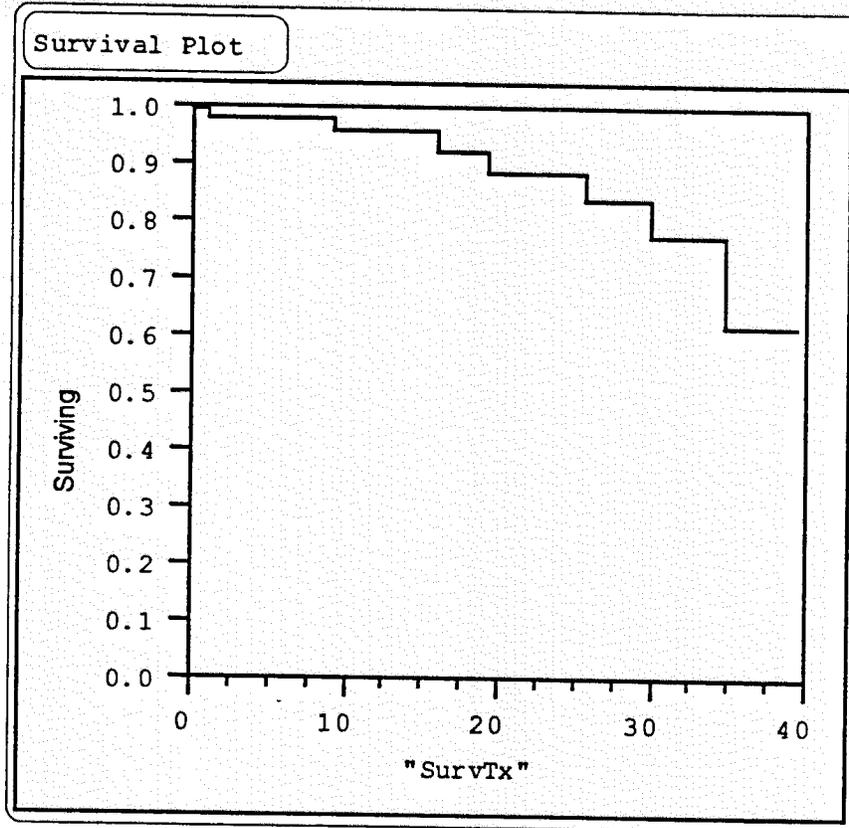
Figure 3. FDA Reviewer's Survival Curve from Date of Diagnosis, CTCL 3



The median survival from the first day of treatment with Uvadex is indeterminate due to lack of data.

Figure 2. FDA Reviewer's Survival Curve from First Day of Treatment CTCL 3

Product-Limit Survival Estimates
Time Variable: "SurvTx"
Censoring Variable: Censoring



SAFETY RESULTS (CTCL 3)

Discontinuation of Therapy (CTCL 3)

The criteria for progression of disease was not defined in the protocol for Study CTCL 3. Of the 12 patients who withdrew due to insufficient/unsatisfactory therapeutic effect, four patients met the criteria for progressive disease as defined in CTCL 1. Eight of the twelve patients had less than 25% increase in overall skin scores during last assessment.

A total of 21 patients withdrew from the study, 7 (33%) of which continued to receive photopheresis with oral methoxalen.

Death on Study (CTCL 3)

One patient died on study. He was a 71 y.o. male diagnosed in at onset in 1991 with exfoliative MF and Sezary syndrome and treated with electron beam therapy and several topical steroid preparation with fair to poor response. His disease progressed to involve the hands, feet, legs, head and face before enrollment to the study. Upon entry, he was noted to have cellulitis of the left leg for which he was taking oral antibiotics.

The patient received photopheresis without incident on November 2 and 3, 1994. He was reported on December 2 to have extensive occlusive vascular disease by arteriography but was deferred due to poor prognosis from aggressive disease. His death on December 4 was considered not related to treatment.

Serious Adverse Events (CTCL 3)

The following table summarizes the serious adverse events reported on study:

Table 22. Serious Adverse Events, CTCL 3

Adverse Event	No. of Patients (n=51)
Cardiovascular	6
Cancer	1
Infection	6
Other Systemic	3
Surgery	2
Exacerbation of CTCL/Other Treatment	3
Accident	1

Summarized from NDA, Table30, vol. 1.24, p. 88

The serious cardiovascular adverse experiences were angina, myocardial infarction. CVA and carotid endarterectomy, arrhythmia, and Hickman catheter thrombosis. Six infections were reported in five patients, two of which were Hickman catheter infections.

Reviewer's comment: There are no serious adverse events related to Uvadex alone, but it is of concern that the extracorporeal administration of Uvadex may be an additional risk for catheter-related infections.

Hematologic Toxicity

Paired t-tests comparing the last value to baseline of certain blood tests showed statistically significant differences (p-value ≤ 0.0001) in the hemoglobin, hematocrit, RBC and potassium.

Reviewer's comment: It is clearly possible for patients to develop anemia and other metabolic abnormalities over time with this treatment. However, such paired analyses of laboratory tests may be misleading and should be interpreted with caution. First, the differences may not necessarily be clinically significant (e.g. median hematocrit at baseline = 41.12 vs. final = 37.99).

Summary of Adverse Events

The sponsor reported adverse events as mild, moderate or severe. There were a total of 185 adverse events, 14 of which were reported as severe. The most frequent reported adverse events include bacterial infection (15), exacerbation of CTCL (13), and loss of venous access (9). No adverse event could be attributed to methoxalen. There was only one incidence of mild nausea. The following table is list of severe adverse events (incidence ≥ 2) and of those events experienced by ≥ 5 patients.

Adverse Event	Severe	Total No. of Patients
CVA	0	5
Bacterial Infection	2	15
UTI	0	5
Pneumonia	2	2
Exacerbation of CTCL	3	13
Lymphadenopathy	0	5
Loss of Venous Access	0	9
Instrument Problems	0	6

Reviewer's comment: The most severe and most frequently reported adverse events were either related to underlying disease of the administration of therapy. There does not seem to be any toxicity in the above table that can be attributed to methoxalen alone.

COMPARISON OF SAFETY RESULTS (CTCL 1 and CTCL 2)

Safety assessments include monthly physical examinations, monthly laboratory evaluations (CBC, SMA, coagulation profile, Coomb's test), periodic pregnancy testing for females, adverse event reporting, and chest x-ray, EKG and eye examinations as needed.

Reporting of adverse events experienced in conjunction with orally administered 8-MOP in studies CTCL 1 and CTCL 2 were combined. The report was based on 39 patients in CTCL 1 and 57 patients in CTCL 2 who received 2540 and 1779 treatments, respectively. The following table summarizes adverse events which were assessed as "related to therapy" for the reporting period between 1983 to April 1992.

**Table 24. Complications Related to Therapy
 CTCL 1 and CTCL 2 (1983- April 1992)**

Type of Complication	No. of Treatments (n=4319)	No. of Patients (n=96)
Fever	17	8
Increased erythema	8	8
Hypotension	5	4
Nausea and vomiting	3	3
Hypovolemia	3	3
Line Infection	3	3
Keratoacanthoma	2	2
Urticaria	2	1
CHF	1	1
Confusion	1	1
Confusion, ↓ O ₂ saturation, fever	1	1
Diarrhea	1	1
Fatigue	1	1
Headache	1	1
IV Infiltration	1	1
LV Failure	1	1
Nausea, vomiting, diarrhea	1	1
Sodium citrate reaction	1	1
Staph sepsis	1	1
Fever post albumin infusion	1	1
Wheezing	1	1

Reviewer's comment: Overall, adverse events from photopheresis with the use of oral 8-MOP in CTCL 1 and CTCL 2 are uncommon, in contrast to reports that as much as 10% of patients taking oral MOP experience nausea/vomiting when used in other indications. The safety advantage of extracorporeal administration of Uvadex may be more difficult to prove and less significant since the incidence of adverse events with 8-MOP is already uncommon. However, one could postulate that 8-MOP related side effects may have been experienced by those patients who achieved higher serum levels of the drug.

FDA REVIEWERS SUMMARY OF BENEFITS, RISKS AND CONCERNS (CTCL 3)

Table 25. Summary of Benefits, Risks, and Concerns (CTCL 3)

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
<i>Study Design and Conduct</i>		
<ul style="list-style-type: none">• Oral 8-MOP FDA approved for the proposed indication• Improved control of study by minimizing confounding factors such as prohibiting treatment with other agents• Accelerated treatment design reflects community practice	<ul style="list-style-type: none">• Single arm, non-randomized phase 2 study• Uncertainty/non-uniformity of treatment schedule• Large drop-out rates due to non-compliance with single therapy• Bias resulting from historical comparisons	<ul style="list-style-type: none">• Difficulty of conducting large, randomized studies in a rare disease such as CTCL
<i>Efficacy</i>		
<ul style="list-style-type: none">• Median Skin Score response of 37%• Improvement in edema, scaling, fissures• Photographic evidence of clinical benefit (edema, scaling, and resolution of skin lesions)• Cell Viability and PHA Stimulation Assay results consistent with results from oral 8-MOP studies• Minimum effective photoactivating bag concentrations of methoxalen reached in 97% of patients	<ul style="list-style-type: none">• Inferior median response compared to oral 8-MOP (CTCL 1 vs. CTCL 3)• Lower limit of the 95% C.I. is below 25%• Shorter duration of response compared to CTCL 1 and 2 due to shorter treatment duration, high drop out rate, shorter follow-up• Non-contributory survival data	<ul style="list-style-type: none">• Uncertainty of extent of use of concomitant medications that may affect skin score assessments
<i>Safety</i>		
<ul style="list-style-type: none">• No evidence of toxicity related to Uvadex alone		<ul style="list-style-type: none">• Device/procedure related toxicities might be increased?

OVERALL EVALUATION AND CONCLUSIONS

Full approval for oral methoxalen/UVAR Photopheresis System was granted by the FDA on May 1988 on the basis of efficacy results shown in 37 patients (CTCL 1) with a follow-up study of 54 patients (CTCL 2) for its use in the palliative treatment of skin manifestations of cutaneous T-Cell Lymphoma in patients who were unresponsive to other forms of treatment. The sponsor now seeks approval for extacorporeal administration of methoxalen for the same indication. Data from a single phase 2 trial which attempted to show direct and indirect evidence of efficacy and improved safety profile were submitted.

The prospectively defined, primary efficacy variable was a body surface area weighted composite of the CTCL involved skin. A successful response to therapy required a 25% reduction in skin score maintained for at least 25 days. The analysis of the intent-to-treat population (n=51) in this single-arm trial showed a response rate of 37% and duration of response of 140 days. The results also suggested that the likelihood of a response to treatment is greatest within six months of starting treatment with a mean time to response of 84 days.

There was a large difference favoring oral 8-MOP in skin score responses in study CTCL1 compared to Uvadex in study CTCL 3 in both the six month treated and the intent to treat analysis group (33% vs. 54% and 37% vs. 74%, respectively). This difference is less pronounced between another oral 8-MOP study, CTCL 2 vs. CTCL 3(28% vs. 33% in the six month treated, and 44% vs. 37% in the ITT group). Although it is possible for oral 8-MOP to be more efficacious than Uvadex, there were several uncontrolled factors that may explain the discrepancies. The mean number of treatments patients received in CTCL 1 and CTCL 2 were substantially more than that received by patients in CTCL 3. Concomitant medications such as systemic steroids were allowed for patients in CTCL 1 and topical steroids for CTCL 2, but were limited to the hands and soles for patients in CTCL 3. Since CTCL is both a systemic and locally debilitating disease, current clinical practice does not limit treatment to a single modality. As such, mandating exclusive use of the experimental drug became a problem that reflected in patients' acceptance and compliance with treatment. An adequate comparison of the response rates between 8-MOP and Uvadex would probably require a large randomized study.

Although not specifically defined in the protocol, the results of the skin score analysis were consistent with the results of the individual analysis of edema, scaling and fissures. These findings are supported by photographs of patients with dramatic improvements such as resolution of lesions, relief of edema and scaling after treatment with Uvadex. Although not documented, it seems likely that these changes also result in other clinical benefit such as relief of pruritus, pain, infection, improving ambulation, etc., and indirectly in terms of delaying or avoiding complications from untreated disease. The evidence for prolonging survival from treatment with Uvadex is not clear. The clinical trials were not designed with survival as an endpoint and the data submitted were insufficient to make these estimates.

Uvadex levels obtained from the photoactivation bags indicate levels that are approximately four times (203 ng/ml vs. 50 ng/ml) the minimum level required for demonstration of activity. In vitro test parameters indicate that on the average, cell viability test results post treatment was below 50% on day 7. On the average, there was 89% inhibition of DNA synthesis in samples taken from the photoactivation bag. Although not indicative of clinical response, these results are consistent with expected levels using oral methoxalen and indicate that the levels of Uvadex were adequate to result in a pharmacodynamic effect in the cells treated.

The results of the study also clearly demonstrate that Uvadex is better tolerated, with essentially no evidence of Cmax related side effects such as nausea, vomiting, diarrhea, etc. seen with oral 8-MOP. However, whether Uvadex/UVAR Photopheresis therapy is a safer alternative is still unconfirmed since device/procedure related adverse events such as line infections, venous thromboses, etc. were also experienced.

Overall, the results of study CTCL3 demonstrate that UVAR Photopheresis/Uvadex methoxalen therapy is a safe and effective alternative to oral methoxalen/photopheresis for the treatment of the skin manifestations of CTCL. A randomized trial comparing the different routes of administration is desirable but not required, to confirm the findings.

Team leader comments: CTCL2 was more recent, was larger, and was better controlled (less use of systemic steroids) than CTCL1. Therefore, it is the appropriate comparator trial for Uvadex. Similarity of efficacy between CTCL2 and CTCL3 has been adequately demonstrated, and the safety profile was acceptable. I recommend approval of this NDA.

IS

Isagani Mario Chico, MD
Medical Officer
Division of Oncology
HFD-150

2/4/99

IS

Grant Williams, MD
Medical Team Leader
Division of Oncology
HFD-150

W 2-5-99

cc:
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HFD-150/Division File
HFD-150/I.M. Chico
HFD-150/D. Catterson