

Diagnosis and Main Criteria for Entry

These only apply to Studies CTCL1 and 3. There were no specific Inclusion and Exclusion criteria written in CTCL 2.

1. Patients 18 years or older. (For CTCL 3: 18-80 years.)
2. Patients with the diagnosis of CTCL based upon one of the following four tests:
 - At least one skin biopsy out of three taken from three different lesions for histological analysis which shows abnormal cells consistent with a diagnosis of CTCL; or
 - One skin biopsy out of three taken from three different lesions which demonstrates T-cell infiltration by fluorescent antibody screening (BE₂, OKT₁, OKT₃, OKT₈)
 - Lymph node biopsy for histological analysis and chromosome (Karyotype) analysis which is consistent with a diagnosis of CTCL; or
 - Peripheral blood smear showing abnormal lymphocytes (Sezary cells)

Reviewer's note: The histologic criteria for inclusion may include patients with a wide range of disease stages. Patients for which peripheral smears were not the basis for diagnosis and inclusion into the study may actually be understaged. Assuming that patients with systemic disease are more resistant to treatment, the response rates to Uvadex could vary widely through selection bias. Nevertheless, it will show whether Uvadex has activity in this disease.

3. Patients that have a progressive disease during the last year. This was defined in study CTCL 3 as an increased extension of disease, or increased skin score, as observed by the patient or the physician.
4. Patients with skin lesions visually consistent with CTCL.
5. Women of childbearing age must be using a primary method of birth control, i.e., oral contraceptives, female sterilization, diaphragm with a spermicide, or have consent to using condoms or male sterilization preceding entry into the study and during the study.
6. Patients on prednisone at the beginning of the study were considered for admission into the study on an individual basis. The investigator and the Extracorporeal Medical Director were to consider the length of time that the patient was on a given dosage of prednisone, as well as the patient's status, when making the decision as to whether to include the patients in the study. For CTCL 3, patients on oral or topical steroids are excluded. Patients who develop fissures on the palms and soles while on study have a limited use of topical steroids and should be documented.
7. For CTCL 3, patients must have adequate veins to provide access.

Patients were excluded for the following reasons: medical problems which would contraindicate photopheresis, photosensitive diseases, hypersensitivity to 8-MOP, progressive deterioration in renal function, pregnancy, continuously elevated SGOT and SGPT, aphakia, coexistent melanoma, basal cell or squamous cell carcinoma, a history of liver damage, CTCL skin tumors without erythroderma or CTCL tumors 5 mm or larger in diameter, clinically evident involvement of the liver, spleen, bone marrow, or other viscera,

overt leukemia, mental incompetence, and pregnancy or nursing a child. Patients could not be on any other experimental drug or device for the treatment of CTCL.

Patient Monitoring

Table 4. Patient Monitoring, CTCL 1

	During Phase 1	Prior to Treatment	After Treatment	Every 6 months	End of Study
H & P	x	x			x
Chest X-ray, EKG	x			x	
Ophthalmologic Exam	x			x	x
CBC and Biochemistry		x	x		x
Coags, Coombs		x			x
ANA ^a	x				x

^a also done three months into the study and whenever the patient experiences symptoms of photosensitivity and hypersensitivity

Note: No schedule for patient monitoring in study CTCL 2.

Table 5. Patient Monitoring, CTCL 3

Frequency	Tests
Baseline	H&P, Informed Consent, 1° and 2° Skin Assessments ^a , Concomitant Meds, AE's, Labs, Serum HCG, HIV Antibody, Hep B Surface Ag, CXR, EKG, Eye Examination, Methoxalen Levels (bag and serum)
Every course	H&P, 1° Skin Assessment, Concomitant Meds, AE's, Labs, Methoxalen Levels (bag and Pt.)
Courses 4, 7, 10,12	2° Skin Assessment, Serum HCG, Cell Viability (bag and Pt), PHA Stimulation (bag and Pt)

^a skin assessments performed by two observers

Removal from Study

There were no criteria for removal of patients from therapy or exclusion of results from assessment in the protocol for CTCL 2. Patients can be removed from studies CTCL 1 and CTCL 3 for the following reasons:

- Patient withdrawal
- Severe adverse reactions
- Uncooperativeness
- Completion of treatment
- Missing two consecutive treatment cycles
- Disease progression

Efficacy Assessment

Definition of Response (CTCL1, 2 and 3)

A response is determined by the following:

1. Skin Response: a 25% reduction in the baseline overall skin lesion score maintained for four consecutive weeks (see below). Skin response assessments were performed by dermatologists.
2. Reduction in Peripheral Lymph Node Size: 50% reduction in lymph node size, determined by calipers, which is maintained for four consecutive weeks.
3. Improvement in Performance Status Classification: improvement in the status classification by one grade level which is maintained for four consecutive weeks.

A **Partial Response** is declared when a successful response is achieved in at least one of the categories on patients admitted to the study with more than one of the presenting categories. A **Substantial Response** is declared when a successful response is achieved in all presenting categories.

Reviewer's comment: The only patients who may qualify for a "Substantial Response" are those with more advanced (Stage 4), disseminated and debilitating disease. No patients with stage 4 disease were enrolled in the studies.

Skin scores were performed according to the following procedure:

Step 1: Body Surface Area is estimated by dividing the body into 29 sections. In CTCL 2, the estimate of the body surface area was based on division of the body into 8 sections.

Step 2: Body Area Severity Score of each body section is rated according to the following scale:

0	Normal Skin
0.5	A background normal with scattered erythematous papules
1	Minimal erythema and edema, no scaling or fissuring
2	Substantial erythema and edema; no scaling or fissuring
3	Submaximal erythema, scaling and edema; no fissuring or ectropion
4	Most severe- universal involvement with maximal erythema, edema and scaling; any fissuring or ectropion

Step 3: Regional Score: Multiply each body surface area severity score by the percentage surface area of that body area to obtain a regional score.

Step 4: Overall Skin Lesion Score: Add all of the regional scores together to obtain the overall lesion score.

Reviewer's comment: For CTCL 1 and CTCL 3, the torso and the back each comprise 18% of the total body surface area. Changes on the lesions located in these areas have a large impact on the overall scores.

The response assessment for skin scores in study CTCL 2 was based on total scores of body surface area that have been divided into 8 sections only; in contrast to 29 sections in studies CTCL 1 and CTCL3. Unless the disease is overly aggressive or highly responsive to treatment (not common in CTCL), the time for declaring changes in tumor status (response or progression) could be longer.

Total body photographs were taken at the following times in CTCL 1, 2, and 3:

- Immediately preceding the first photopheresis treatment of Phase II
- Whenever there was a 25% or greater change from baseline in the overall skin score
- Whenever skin tumors required concomitant therapy.
- Whenever a patient was released from study.

Reviewer's comment: The method of photographic documentation was not adequately described. Detailed instructions on proper identification of lesions, lighting, equipment, etc, should have been provided in the protocol. The schedule of picture taking is based on subjective parameters such as overall skin lesion

response status and use of concurrent medications. As such, subtle but important clinical changes could have been missed.

Monitoring of the peripheral blood for malignant cells done according to the same schedule as the skin assessment scores:

- Immunologic marker OKT3, OKT4, OKT8 BE1 and BE2
- Morphologic examination for Sezary cells
- Chromosome markers (karyotype analysis)

Statistical Considerations, Study CTCL 3

The proportion of patients enrolled that successfully responded to treatment were compared to the response rate reported in the oral methoxalen study (CTCL1) which revealed a 21/30 (53.9%) response rate within six months of initiation of therapy. The lower and upper 95% confidence intervals were 31% and 70%, respectively. For study CTCL3, a target sample size of 42 was recommended since the lower bound of the 95% confidence interval exceeds the observed lower boundary obtained with oral methoxalen (29%) and exceeds the lower 95% confidence limit of 25%.

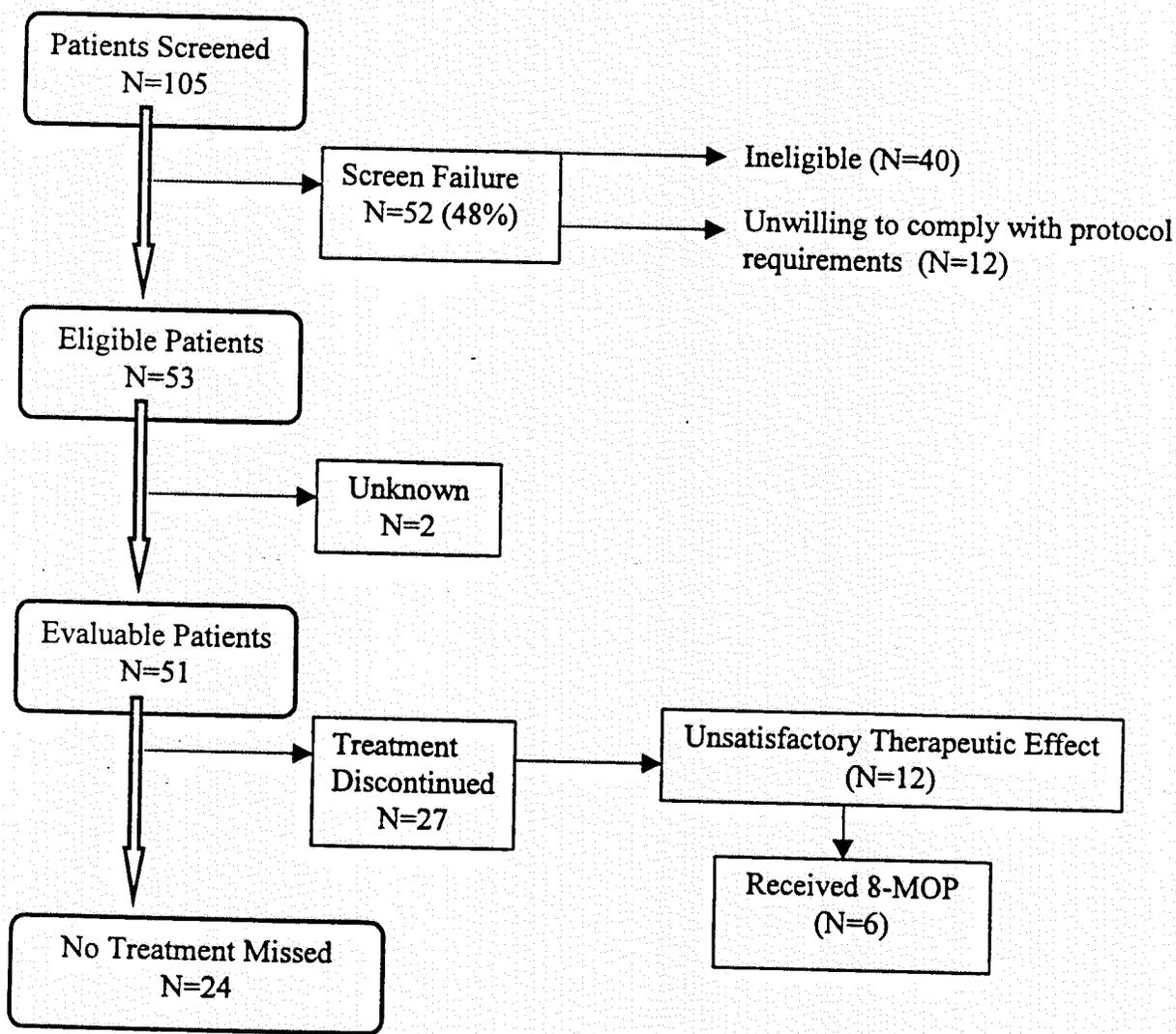
The proportion of patients that successfully respond to treatment will be compared via inference to the response rate observed over the equivalent time period with oral methoxalen. If the lower 95% binomial interval is greater than 25%, treatment with Uvadex will be considered effective. This target was derived from the assumption of 10% spontaneous remission rate and 15% improvement.

STUDY RESULTS (CTCL 3)

Reviewer's comment: The presentation of the study results (Efficacy and Safety) is divided into two parts. A more detailed presentation and analysis of the pivotal trial (CTCL 3) is followed by a comparative analysis of the results from the three studies.

Patient Disposition

Figure 1. Patient Disposition- CTCL 3



Reviewer's comment: The eligibility criteria and rules regarding concurrent therapy were strictly enforced in CTCL 3. Of twelve patients who were unwilling to comply with protocol requirements, six refused to be limited to only one therapy. There were also twelve patients who discontinued treatment due to unsatisfactory therapeutic effect, six of which proceeded to receive oral 8-MOP. Five patients were suspected of protocol violations for using topical or systemic steroids while on study. There were 21 of 51 patients who withdrew prior to completing the treatment period required by the protocol. This occurred because patients required additional concomitant therapy, such as topical steroid creams which was prohibited by the study protocol.

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.

Patient Demographics (CTCL 3)

Table 6. Patient Demographics

Variable	CTCL 3 (N=51)
Mean Age	62
Race (%)	
Caucasian	44 (86)
Black	7 (14)
Mean Age at Date of First Treatment	63
Gender (M/F) %	34/17
Mean No. of Prior Therapies	4.3

Reviewer's comment: Patient Enrollment According to Disease Stage (%): Stage I: 15 (29%), Stage II: 6 (12%); Stage III: 30 (59%); Stage IV: 0.

Treatment Compliance (CTCL 3)

There were 35/51 patients (69%) who continued treatment beyond 180 days and completed both phases of the study. Follow-up information is available only for 43/51 (84%) of the

patients. The most common reason for terminating therapy in 27/43 (63%) of the patients is to receive oral 8-MOP or other therapies that are not allowed in the study.

Post-Study Treatments

The following table summarizes the subsequent treatments patients enrolled in CTCL 3 received. Most of the patients were given oral 8-MOP.

Table 7. Post-Study Treatments (CTCL 3)

Treatment	No. of Patients (N=51)
Oral Crystalline 8-MOP/UVAR	27
Anti-Neoplastics	8
PUVA	8
Topical Steroids	7
Systemic Steroids	6
Interferon Alpha	5
NSAID	4
Total Body Electron Beam Radiation	3
Emollients	2
Retinoids	1
DAB 389- IL-2 Fusion Toxin	1

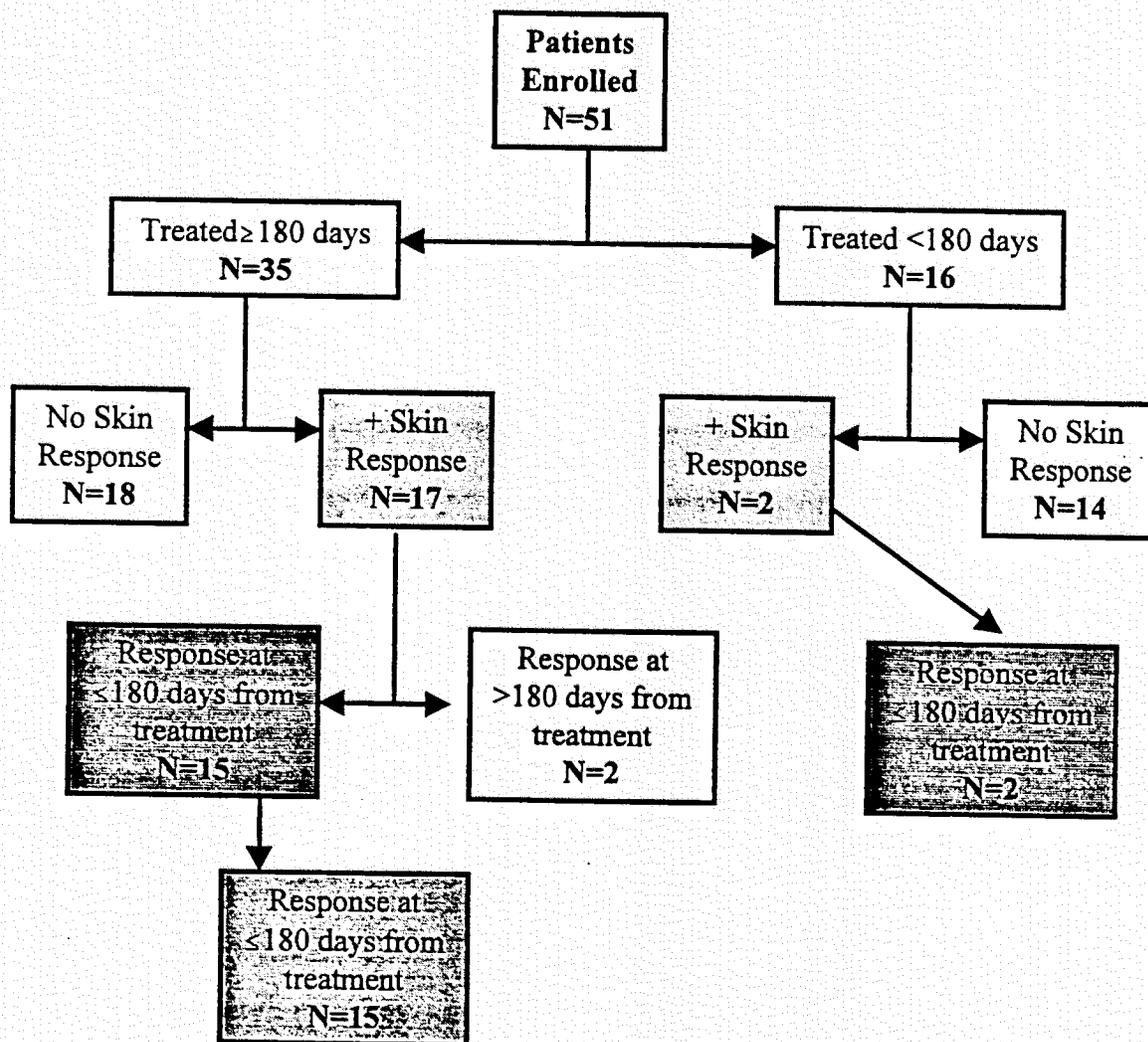
Reviewer's comment: The motivation to stay on study was low with patients not being allowed to use other medications, especially those that relieve local symptoms. Since oral 8-MOP was available, it is understandable why a majority of patients dropped off and continued with standard, approved therapy of the same drug.

EFFICACY (CTCL 3)

Sponsor's Analysis of Tumor Response

Each patient will be evaluated according to the TNM classification scheme at the time of admission into the study.

Figure 2. Flow Chart of Skin Score Response (CTCL 3)



Reviewer's comment: There were 19 (37%) patients who responded to Uvadex, most of which occurred within six months (180 days) of the start of treatment (17 patients). There were 18 patients who did not respond and only two patients who responded after receiving treatment exceeding 180 days. These results suggest that

the likelihood of success with the use of Uvadex are seen within the first six months of treatment.

Concomitant Medications

The most frequent medications used during the study includes the following:

Table 8. Concomitant Medications (CTCL 3)

Medication	No. of Patients
Hydroxyzine	29
Triamcinolone Cream ¹	17
Aspirin	16
Aquaphor Topical Ointment	16
Doxepin	11

¹ use limited to palm of hands and soles of feet

Reviewer's comment: The protocol instructions to use triamcinolone exclusively for the hands and soles may be problematic as patients could apply the ointment on any surface if they desired.

Electronic data and paper listings on concomitant medications were reviewed for the frequency of use of concomitant medications on patients who responded to Uvadex versus the total population of patients treated.

**Table 9. Concomitant Medications in Responders (CTCL 3),
FDA Analysis**

Medication	No. of Patients N=51	Responders N=19
Hydroxyzine	29	11
Triamcinolone Cream ¹	17	9
Topical Ointment	16	6

¹ use limited to palm of hands and soles of feet

Despite strict implementation of protocol rules, there is still concern that the assessment of skin scores may be affected by the above medications through their anti-inflammatory, antipruritic and lubricating properties. It is important in future studies to attempt determine whether Uvadex itself contribute to the relief or prevention of local symptoms and complications.

The skin stage has been thought of as probably the most important risk factor for response to treatment in this disease. Responding and non-responding patients were grouped according to the skin stage at study entry with the following results:

Table 10. FDA Analysis of Pre-Treatment Skin Stage (CTCL 3)

Skin Stage	Total (%) (N=51)	Responders (%) (N=19)	Non-Responders (%) (N=32)
I	15 (29)	10 (66)	4 (27)
II	6 (12)	1 (17)	5 (83)
III	30 (59)	8 (27)	22 (73)
IV	0	0	0

Of the responders, 66% had stage 1 and 27% had Stage 3 disease which was about the reverse for non responders, which had 73% of the patients with stage 3 disease and 27% with Stage 1. There were no patients with Stage 4 disease enrolled in the clinical trial. The mean length of response are as follows: Stage 1: 147 days (28,288), Stage 2: 28 days and Stage 3: 131.7 days (29-301). There seems to be an inverse correlation between stage and skin score responsiveness to Uvadex; although the length of response seems to be less affected.

Time to Response and Duration of Response

Table 11. Time to Response and Duration of Response (CTCL 3)

Type Of Response	Median Days to Response (95% C.I.)	Median Days of Response (95% C.I.)
ITT Response within 6 months	84 (35,116)	140 (56,245)
ITT Overall Response	86 (36,117)	140 (56,224)

Summarized from NDA, Tables 23-25, vol.1.24, p. 69

Reviewer's comment: The similarities in results between the three groups confirm the opinion that prolonging the treatment with Uvadex beyond 180 days or six months does not provide additional benefit as regards rate and duration of lesion response.

Improvement in Edema, Scaling and Fissures

Edema was scored as present or absent for each body area at baseline and at each treatment. The criteria used to evaluate edema and scaling were prospectively defined in "Body Area Severity Score" where involved skin lesions are rated from 0 to 4 depending on the presence and severity of papules, erythema, edema, scaling, fissuring and ectropion. The following analyses were not prospectively defined.

Reviewer's comment: Body areas were conservatively rated according to presence or absence of edema and scaling. As such, an observation of "absence of edema" would require a change in severity score from "≥1" to "0"; "absence of scaling" would require a change in score from "≥3" to "≤2"; and "absence of fissures" would require a change in score from "4 to ≤3".

Table 12. Improvement in Edema, ITT Overall (CTCL 3)

ITT Overall	Mean ± SD (n)		
	Baseline	6 Months	≥ 300 Days
Responders	11.3 ± 9 (19)	6.1 ± 9.3 (17)	3.3 ± 7.2 (17)
Non-Responders	15.3 ± 10.5 (32)	13.8 ± 10.9 (18)	12.9 ± 12.3 (14)
Total	13.8 ± 10 (51)	10.1 ± 10.7 (35)	7.6 ± 10.8 (31)

Summarized from NDA, Table 28, vol. 1.24, p.71

Table 13. Improvement in Scaling, ITT Overall (CTCL 3)

ITT Overall	Mean ± SD (n)		
	Baseline	6 Months	≥ 300 Days
Responders	12.3 ± 10.4 (19)	6.0 ± 8.8 (17)	2.9 ± 4.1 (17)
Non-Responders	18.4 ± 10.6 (32)	19.6 ± 11.7 (18)	2.9 ± 4.1 (14)
Total	16.1 ± 10.8 (51)	13.0 ± 12.3 (35)	10.4 ± 11.5 (31)

Summarized from NDA, Table 28, vol. 1.24, p.73

Table 14. Improvement in Fissures, ITT Overall (CTCL 3)

ITT Overall	Mean ± SD (n)		
	Baseline	6 Months	≥ 300 Days
Responders	1.6 ± 2.7 (19)	0.2 ± 0.5 (17)	0 (17)
Non-Responders	5.8 ± 8.2 (32)	10.8 ± 11.4 (18)	9.1 ± 10.4 (14)
Total	4.3 ± 6.9 (51)	5.4 ± 9.5 (35)	4.1 ± 8.2 (31)

Summarized from NDA, Table 28, vol. 1.24, p.75

Reviewer's comment: Changes in the status of edema, fissures and scaling directly affect the patients' quality of life; therefore, identification of improvements in these parameters is extremely important. The downside of this analysis is its insensitivity to changes in the degree of edema and/or scaling and its inability to clearly define the actual number of patients who derived benefit. This is of special concern in small studies such as CTCL 3. Overall, there seems to be some evidence of clinical improvement in edema, scaling and fissures especially for patients who responded to treatment. A well-controlled randomized study can confirm this.

Other Evidence of Efficacy

Drug Concentration and Relationship to Response

Drug concentration is only related to the amount of methoxalen and UVA light necessary to affect the cell viability and PHA in vitro tests. There is no direct correlation to patient response. A total of 816/819 (97%) of samples from the photoactivation bag were > 50 ng/mg. There were 3/819 (0.4%) samples < 50 ng/ml and 40/819 (5%) samples > 270 ng/ml. Uvadex methoxalen levels in the photoactivation bag had a mean level of 203 ng/ml. The mean Uvadex levels from the patients was 22.6.

Reviewer's comment: The mean Uvadex levels in the photoactivation bag is approximately four times that which has been shown to be efficacious (in vitro), while the mean patient plasma Uvadex levels were approximately five to ten times lower than the levels where Cmax related and the most common symptoms of nausea and vomiting were usually observed. These results are encouraging from the point of being regarded as surrogates for both safety and efficacy of Uvadex.

Cell Viability Monitoring Results

The average inpatient cell viability taken from the buffy coat bag showed a decrease of less than 50% after seven days of treatment. These are results similar to the photopheresis treated cells of patients who received oral 8-MOP. The average of the intra-patient averages is given in the following table:

Table 15. Intra-Patient Cell Viability Results

	Average Counts (Pre-Treatment)	
	Patient's Blood	Buffy Coat Bag
Test Day 0	96.1	92.7
Test Day 3	83.3	65.3
Test Day 7	73.0	46.7

(from NDA 20,969 vol. 1.24, p.60)

PHA Stimulation Monitoring

PHA Stimulation was determined on samples of the patients' blood taken pre-treatment and from the buffy coat bag post-treatment. The average inpatient value was 89.6%.

COMPARISON OF EFFICACY RESULTS

Reviewer's comment: Data in the following section should be interpreted with caution since the studies are small, and with full recognition of the weaknesses of historical comparisons. A randomized trial would be the ideal setting.

Patient and Disease Characteristics:

Table 16. Patient Demographics

Variable	CTCL 1	CTCL 2 (N=57)	CTCL 3 (N=51)
Mean Age	57	63.2	62
Race (%)			
Caucasian			44 (86)
Black			7 (14)
Duration of Disease (years)	1.4	2.4	
Gender (M/F) %	28/12	34/23	34/17
Mean No. of Prior Therapies	3.7	3.3	4.3
Mean 8-MOP dose (mg)	54.12	47.36	--

(summarized from NDA 20,969 vol. 14 (p.31), 21 (p. 33), 24 (p. 52))

Skin Score Responses

Table 17. A Comparison of the ITT Response Within 6 Months (CTCL 1, 2, and 3)

Study	Response n (%)	Binomial 95% CI
CTCL 3 (UVADEX)	17/51 (33)	21 to 48
CTCL 2 (Oral 8-MOP)	16/57 (28.1)	17 to 41.5
CTCL 1 (Oral 8-MOP)	21/39 (53.9)	37.2 to 69.9

Source: CTCLCSR3.doc, Table 20; CTCLCSR2.doc, Table 6; CTCLCSR1.doc, Table 7.

Table 18. A Comparison of ITT Overall Response (All Scores)

Study	Mean # Treatments	Response n (%)	95% CI
CTCL 3 UVADEX)	20.2	19/51 (37)	24 to 52
CTCL 2 (Oral 8-MOP)	31.2	25/57 (43.9)	30.7 to 57.6
CTCL 1 (Oral 8-MOP)	63.5	29/39 (74.4)	57.9 to 87.0

(From CTCLCSR3.doc, Table 22; CTCLCSR2.doc, Table 9; CTCLCSR1.doc, Table 10)

Reviewer's comment: (1) Comments on response rates

Note that the skin lesion response for study CTCL 3 was greater than projected as a significant response (25% vs 33% in the study). However, the lower bound of the 95% confidence interval was only 21%. The ITT Overall Response shows the lower bound of the 95% confidence interval to be closer to 25%.

The difference in the response rates between studies is larger when the intent to treat group analysis is considered. Although it is possible for one to interpret that oral 8-MOP is more efficacious than Uvadex, there were uncontrolled factors that may account for the discrepancies. (1) The mean number of treatments patients in CTCL 1 and CTCL 2 received are 63.5 and 31.2 respectively compared to 20.2 treatments for patients in CTCL 3 (NDA 20969, Table 20, vol. 12, p. 174). (2) Systemic steroids were allowed for patients in CTCL 1 and topical steroids for CTCL 2. Patients who require systemic steroids were excluded and topical steroids were allowed only for application on the palms and soles in CTCL 3. Overall, an adequate comparison of the response rates between 8-MOP and Uvadex would probably require a large randomized study.

Reviewer's comment (2) Analysis of Photographs:

The sponsor submitted photographs on 11 patients from study CTCL 1. These were selected to show significant changes such as disappearance of lesions, decrease in erythema, edema, scaling, resolution of ulcerated lesions, etc in individual patients. The evidence of clinical benefit for the 11 patients receiving 8-MOP was clear.

Photographs of all 51 patients in study CTCL 3 were submitted. There was no standardized and scientific method of photography defined in the protocols as evidenced by inconsistency in technique and in follow-up of lesions. Patients who did not respond to therapy did not have follow-up photographs taken. It was not possible to confirm the skin lesion scores and response assessments.

Changes in lesions that may have some clinical benefit impact were noted for patients in CTCL 3, especially for the "responders" since they were the only group of patients with follow-up photographs. Aside from disappearance of lesions in some cases, there was note of disappearance of scaling, decrease in erythema, edema and swelling of fingers and toes, groin and face of patients who had concurrent skin score responses. This provides objective confirmatory evidence of clinical improvement for these patients.