CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-969

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

OCT 29 1998

NDA#: 20-969

Applicant: THERAKOS, Inc.

Name of Drug: UVADEX sterile liquid 20mg, I.V. for extracorporeal administration

Indication: For use with the UVAR photopheresis system in the palliative treatment of the skin manifestations of CTCL

Document Reviewed: Submission received on 02-27-98 and 04-20-1998

Medical Officer: Isagani Chico, M.D.

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I. BACKGROUND

UVADEX (Methoxsalen, 8-methoxypsoralen) is a photoactive substance found in the seeds of Ammi majus plant. Its pharmacological mechanism of action is to form covalent bonds with DNA leading to inhibition of DNA synthesis, cell division and edpidermal turnover. UVADEX (oral 8-MOP) was approved for oral use in the treatment of patients with severe, recalcitrant psoriasis, for repigmentation of idiopathic vitiligo, and for the palliative treatment of skin manifestation of Cutaneous T-cell Lymphoma, or CTCL.

In this NDA, the sponsor seeks approval of UVADEX Sterile Solution in combination with UVAR Photopheresis System to extracorporeally use in the palliative treatment of skin manifestation of CTCL.

One study used UVADEX Sterile Solution extracorporeally in combination with UVAR Photopheresis System (CTCL 3). The other two (2) studies (CTCL 1 and CTCL 2) were conducted using the currently approved UVAR Photopheresis System with oral administration of 8-MOP. CTCL 3 was a single arm , prospective, multicenter, non-blinded trial. This review will focus on study CTCL 3.

II. BRIEF DESCRIPTION OF STUDIES

Study CTCL 3

Study CTCL3 was a multicenter, single arm, open-label trial of UVADEX Sterile Solution in combination with UVAR Photopheresis System to extracorporeally use in the palliative treatment of skin manifestation of cutaneous T-cell lymphoma, or CTCL, in patients who have been unresponsive to other forms of treatment.

The primary endpoint was a body surface area weighted composite of the severity of CTCL involved skin. The primary objective of this trial was to assess the outcome of successful patients who response to the therapy. A successful response, defined by protocol, was a 25% reduction in skin score maintained for greater than 25 days.
Secondary efficacy endpoints were the duration of response, time to response and survival.

A total of 51 patients were enrolled. The sample size was determined by assuming that 40% sample successful rate with a low 95% bound exceeding 25%. No interim analysis was planned. The protocol specified analysis for the primary endpoint was the intention - to-treat analysis for the response within six-months of treatment.

Study CTCL 1 and CTCL 2

Similar to the CTCL 3, Study CTCL1 and CTCL 2 were multicenter, single arm, open-label trials. But the study drug was the approved oral UVADEX in combination with UVAR Photopheresis System in the similar patient population. Study CTCL 1 was submitted for the approval of the oral UVADEX (oral 8-MOP) and Study CTCL 2 was the follow-up of the CTCL 1.

The primary endpoints for Study CTCL 1 and CTCL 2 were the same as Study CTCL 3, body surface area weighted composite of the severity of CTCL involved skin. The primary objective of these two trials was to assess the outcome of successful patient who response to the therapy. A successful response, defined by protocol, was a 25% reduction in skin score maintained for greater that 25 days.

A total of 57 patients were enrolled in the CTCL 1 and 37 patients were followed in the CTCL 2. The protocol specified analysis for the primary endpoint was the intention -to-treat analysis for the response within six-months of treatment.

III. SUMMARY OF EFFICACY RESULTS AND COMMENTS

This section will summarize the intention to treat analysis results for study CTCL 3 and study CTCL 1 and CTCL 2. The intention to treat patient population was all patients who enrolled into the studies.

Study CTCL 3

Primary Efficacy Endpoint

The primary efficacy endpoint for study CTCL 3 was a body surface area weighted composite of the severity of CTCL involved skin (Skin score). The primary objective of this trial was to assess the outcome of successful patients who response to the therapy. A successful response, defined by protocol, was a 25% reduction in skin score maintained for greater than 25 days. During the treatment phase of the protocol, each patient received one photophresis treatment on two consecutive days every 4 to 5 weeks for a total of 7 cycles.

The response was analyzed using the following three patient populations:

1). Patients responded to the treatment within 180 days (6 months) of initial treatment, regardless of the length of treatment (6 months Intention-to-treat within 6 month response, primary analysis).

2). Patients responded to the treatment within 180 days (6 months) of initial treatment in patients who received at least 180 days of the treatment (evaluable patient population).

3). Patients responded to the treatment any time during the treatment period, regardless of the length of treatment (overall ITT response).

The sponsor's results for the primary endpoint are summarized in the Reviewer's Table III.1.

Reviewer's Table III. 1. Sponsor's Analysis for Primary Efficacy Endpoint

	Responders	Non-responders	95% CI for Response Rate
6 month ITT (n=51)	17(33%)	34(67%)	21%-48%
Overall ITT (n=51)	19(37%)	32(63%)	24%-52%
6 month treated (n=35)	15(43%)	20(57%)	26%-61%

Secondary Efficacy Endpoints

The secondary efficacy endpoints were the duration of response, time to response and survival. The results in the Reviewer's Table III.2. and Table III.3 are based on the sponsor's analyses using the definitions described in the NDA submission for these secondary endpoints.

1. Time to Response

Reviewer's Table III. 2. Sponsor's Analysis for Time to Response (days)

	Median	95% CI
6 month IIT (n=17)	84	35-116
Overall IIT (n=19)	86	56-117
6 month treated (n=15)	86	35-116

2. Duration of Response

Reviewer's Table III. 3. Sponsor's Analysis for Duration of Response

	Median	95% CI
6 month IIT (n=51)	140	56-245
Overall IIT (n=51)	169	119-245
6 month treated (n=35)	140	56-224

3. Survival

The survival analysis was conducted using all 51 patients. The median survival time from the time of diagnosis for these 51 patients was 3790 days (124.6 months) with 95% CI lower bound 1280 days or 42.1 months (upper bound undetermined).

Study CTCL 1 and CTCL 2

Study CTCL1 and CTCL 2 were multicenter, single arm, open-label trials. The study drug was the approved oral UVADEX in combination with UVAR Photopheresis System in patients with CTCL. Study CTCL 1 was submitted for the approval of the oral UVADEX (oral 8-MOP) and Study CTCL 2 was the follow-up of the CTCL 1 as well as the first 50 CTCL patients treated after PMA approval.

Study Results

The endpoints selected for studies CTCL 1 and CTCL 2 were the same as those defined in study CTCL 3.

The sponsor's results based on the three patient populations (see page 3 of this review) are summarized in the following three Reviewer's tables.

Reviewer's Table III. 4. Sponsor's Analysis for Primary Efficacy Endpoint : Response Rate

		Responders	Non-responders	95% CI for Response Rate
6 month ITT	CTCL 1 (n=39)	21(53.8%)	18(46.2%)	37.2%-69.9%
	CTCL 2 (n=57)	16(28.1%)	41(71.9%)	17.0%-41.5%
Overall ITT	CTCL 1 (n=39)	29(74.4%)	10(25.6%)	57.9%-87.0%
	CTCL 2 (n=57)	25(43.9%)	32(56.1%)	30.7%-57.6%
6 month treated	CTCL 1 (n=33)	21(63.6%)	12(36.4%)	45.1%-79.6%
	CTCL 2 (n=43)	14(32.6%)	29(67.4%)	19.1%-48.5%

Reviewer's Table III. 5. Sponsor's Analysis for Time to Response (days)

		Median	95% CI
6 month IIT	CTCL 1 (n=21)	103	76-126
	CTCL 2 (n=16)	70.5	68-153
Overall IIT	CTCL 1 (n=29)	126	92-153
	CTCL 2 (n=25)	153	70-257
6 month treated	CTCL 1 (n=21)	103	76-126
	CTCL 2 (n=14)	81.5	68-153

Reviewer's Table III. 6. Sponsor's Analysis for Duration of Response (days)

		Median	95% CI
6 month IIT	CTCL 1 (n=21)	419	159-896
	CTCL 2 (n=16)	103.5	35-318
Overall IIT	CTCL 1 (n=29)	365	147-637
	CTCL 2 (n=25)	152	76-276
6 month treated	CTCL 1 (n=21)	419	159-896
	CTCL 2 (n=14)	232.5	119-454

The survival analysis was conducted using the 39 patients in study CTCL 1. The median survival time from the time of diagnosis for these 39 patients was 126.9 months with 95% CI of 60.2-130.2 months.

Summary and Conclusions:

Given the uncontrolled natural of study CTCL 3 and the relative small sample size, no formal statistical testing can be conducted. Therefore, any claims of "improvement" or "as effective as" need to be made cautiously. The definitive conclusion should only be based on clinical judgment.

/S/

Ning Li
Biostatistician

Concur:

Dr. Chen /S/

Dr. Chi

cc:
Archival: NDA20-969
HFD-150/Dr. Chico
HFD-150/Dr. Williams
HFD-150/Dr. Justice
HFD-150/Ms. Vaccari
HFD-150/Ms. Catterson, Project Manager
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Chen
HFD-710/Dr. Li
HFD-710/chron

This review consists of 7 pages of text.

LI/10/29/98 MSWD "C:/DATA/WORDFILES/NDA20969.DOC".

Ms. Catherson

Statistical Review and Evaluation

Review of Stability Data

NOV 30 1998

NDA#: 20-969

Applicant: THERAKOS, Inc.

Name of Drug: UVADEX sterile liquid 20mg, I.V. for extracorporeal administration

Indication: For use with the UVAR photopheresis system in the palliative treatment of the skin manifestations of CTCL

Document Reviewed: Submission received on 04-30-1998

Chemistry Reviewer: Y. Hsieh

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I. BACKGROUND

UVADEX (Methoxsalen, 8-methoxypsoralen) is a photoactive substance found in the seeds of Ammi majus plant. Its pharmacological mechanism of action is to form covalent bonds with DNA leading to inhibition of DNA synthesis, cell division and edpidermal turnover. UVADEX (oral 8-MOP) was approved for oral use in the treatment of patients with severe, recalcitrant psoriasis, for repigmentation of idiopathic vitiligo, and for the palliative treatment of skin manifestation of Cutaneous T-cell Lymphoma, or CTCL.

In this application, the sponsor seeks approval of UVADEX Sterile Solution for a 24 month shelf life (expiration dating period). The submission contains data of three batches with up to 18 month stability data. This review is restricted to the analysis of potency assay data.

II. Sponsor's results

The sponsor provided the stability data for the three validation batches of UVADEX produced at The sponsor's finding's are summarized in Table 1.

Table 1. Estimated expiration Dating Period
(Linear Regression Analysis Estimates)

	Potency		Total Impurity	
	Upright	Inverted	>24 mos	>24 mos
Batch 1	>24 mos	>24 mos	>24 mos	>24 mos
Batch 2	54 mos	52 mos	>24 mos	>24 mos
Batch 3	67 mos	64 mos	>24 mos	>24 mos

Figure 1 and Figure 2 show the sponsor's potency analysis results for the fitted three regression lines for both upright and inverted product.

III. Reviewer's Comment

The sponsor's statistical approach was appropriate. The sponsor's requested 24 months expiry period is supported by the data submitted as well as the statistical analysis results.

IV. Summary

The sponsor's requested 24 months expiry period is supported by the data submitted as well as the statistical analysis results. However, due to the limited data points submitted and the natural of the chemical compounds, the decision can only be made based on chemistry judgment.

/S/

Ning Li
Biostatistician

Concur:

Dr. Chen

Dr. Chi /S/

cc:
Archival: NDA20-969
HFD-150/Dr. Wood
HFD-150/Dr. Hsieh
HFD-150/Ms. Catterson, Project Manager
HFD-710/Dr. Chi
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HFD-710/Dr. Li
HFD-710/chron

This review consists of 3 pages of text.
LI/11/12/98 MSWD "C:/DATA/WORDFILES/NDA20969s.DOC".

REVIEW TO HFD-150
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGY REVIEW OF NDA
MAY 13, 1998

MAY 13 1998

A. NDA 20-969

PRODUCT NAME: UVADEX®
APPLICANT: THERAKOS, INC.

B. 1. DOSAGE FORM: Sterile Solution (20 µg/mL)

2. METHODS OF STERILIZATION:

3. PHARMACOLOGICAL CATEGORY/PRINCIPAL INDICATION: Oncology drug

C. 1. DATE OF SUBMISSION: February 20, 1998
2. ASSIGNED FOR REVIEW: May 1, 1998
3. DRUG PRIORITY: 1S (desired completion May 25, 1998)

D. REMARKS: Validation of the is in the CMC section of the submission. The drug product is

E. CONCLUSIONS: The NDA 20-969 which provides for UVADEX® is recommended for approval from the standpoint of product quality microbiology.

/S/ 5/13/98

Patricia F. Hughes, Ph.D.
Microbiology Reviewer

PH 5/13/98

cc.: Original NDA 20-969
HFD-150/Div.Files
HFD-150 YHsieh
HFD-/DCatterson
HFD-805/PF Hughes
HFD-160/DivFiles
Drafter by PFHughes/5/13/98
R/D initialed by PHCooney