

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-415**

**STATISTICAL REVIEW(S)**



## STATISTICAL REVIEW AND EVALUATION

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## **1. EXECUTIVE SUMMARY**

### **1.1 Conclusion and Recommendations**

Two pivotal trials (studies PC T305 and PC T306) and two Phase 3 trials (studies PC T301 and PC T302) were submitted in support of the efficacy claim of Metvix PDT therapy. All enrolled subjects are Caucasians.

The efficacy claim of two sessions of Metvix PDT in the treatment of mild to moderate actinic keratoses (AK) lesions on the face or scalp is supported in each of studies PC T305 and PC T306 in terms of the percentage of subjects with 100% of all lesions cleared.

### **1.2 Overview of the Clinical Program and Studies Reviewed**

The study drug product is Metvix Cream, which is designed for a topical use in conjunction with the photodynamic therapy (PDT), in the treatment of mild to moderate non-hyperkeratotic actinic keratoses (AK). The treatment starts with the cream application to AK lesions for approximately 3 hours, followed by illumination procedure.

Efficacy results from four Phase 3 trials were submitted in the statistical section of the Sponsor's NDA submission. Among the four trials, the Sponsor designated studies PC T305 and PC T306 as the pivotal trials, and studies PC T301 and PC T302 as supportive trials.

The two pivotal trials were conducted in Australia (study PC T305) and US (study PC T306) between March 2000 and February 2001. Total of 204 and 80 subjects were enrolled from 9 and 5 centers, respectively, in studies PC T305 and PC T306. The enrolled subjects in study PC T305 were randomized into Metvix PDT, cryotherapy and placebo PDT groups. This resulted in 91, 90, and 23 subjects in the three treatment arms. For study PC T306, 42 and 38 subjects were treated with Metvix PDT and placebo PDT, respectively.

Studies PC T301 and PC T302 were conducted in Europe during April 1999 and January 2000. Total of 202 and 39 subjects were enrolled from 13 and 4 centers in studies PC T301 and PC T302, respectively. For study PC T301, 102 and 100 subjects were treated with Metvix PDT and cryotherapy; while 20 and 19 subjects were assigned to Metvix PDT and placebo PDT in study PC T302.

It should be noted that two treatment sessions of PDT with 7-day apart were performed on the lesions of the face or scalp in the pivotal trials PC T305 and PC T306, but only 1 session of PDT was applied to lesions on the face or scalp in studies PC T301 and PC T302.

### **1.3 Principal Findings**

Efficacy results from studies PC T305, PC T306, PC T301 and PC T302 are presented in Table E.1 below.

**Table E.1: Summary of Efficacy Results**

Pivotal	Efficacy endpoints	Metvix PDT	Placebo PDT	Comparison
Study 305	<b>Primary:</b> Patient complete response rate	71/88 (81%)	3/23 (13%)	< 0.001
	<b>Secondary:</b> Patient excellent response rate	76/88 (86%)	4/23 (17%)	< 0.001
	Lesion complete response rate	317/360 (88%)	21/74 (28%)	< 0.001
Study 306	<b>Primary:</b> Patient complete response rate	33/42 (79%)	8/38 (21%)	< 0.001
	<b>Secondary:</b> Patient excellent response rate	35/42 (83%)	12/38 (32%)	< 0.001
	Lesion complete response rate	221/260 (85%)	92/242 (38%)	< 0.001
<b>Supportive Phase 3 Trials</b>				
Study 301	Patient complete response rate	46/98 (47%)	N/A	N/A
	Patient excellent response rate	54/98 (55%)		
	Lesion complete response rate	252/367 (69%)		
Study 302	Patient complete response rate	11/19 (58%)	2/18 (11%)	< 0.001
	Patient excellent response rate	11/19 (58%)	2/18 (11%)	< 0.001
	Lesion complete response rate	32/49 (65%)	6/36 (17%)	< 0.001

Pivotal Trials PC T305 and PC T306

The demographic characteristics of the enrolled patients were:

- Between 31 and 89 years old with median age of 68 and 66 in studies PC T305 and PC T306, respectively.
- All enrolled subjects are Caucasians.
- More than 60% of enrolled subjects had less than 4 AK lesions at baseline in study PC T305; while all subjects in study PC T306 had 4-10 AK lesions.

The baseline lesion characteristics were:

- All AK lesions were located on the face or scalp, with 80% vs. 84% of lesions on the face for Metvix vs. placebo group.
- Approximately 65% of lesions were mild in severity at baseline in Metvix PDT group, as compared to 62% in placebo PDT arm.

The intent-to-treat (ITT) analysis, treating missing data as failures, showed the superiority of Metvix PDT over placebo PDT in the treatment of mild to moderate AK lesions on the face or scalp with respect to patient complete response rate 3 months after treatment (p-value < 0.001).

Other comments for studies PC T305 and PC T306 are:

▪ Study PC T306:

- Investigators might be able to differentiate the treatment assignment at the visit of the 2<sup>nd</sup> treatment session even though nurses administered illumination and recording of local adverse events. This is because two sessions were only 7 days apart. The adverse events (i.e. crusting, blisters, erythema, and burning sensation skin) resulted from the 1<sup>st</sup> session might not be well resolved by the time of the 2<sup>nd</sup> treatment session. However, sensitivity analyses show that Metvix PDT is overall better than placebo PDT even if the susceptible subjects are imputed as failures.

- **Study PC T305:**
  - Blinding might be an issue even though the lesion response was evaluated 3 months after treatments, as the investigators rather than other party handled the illumination procedure and recording of local adverse events. However, efficacy results show the consistency of response rates for Metvix between studies. The respective response rate is 81%, 86%, 88% for patient complete response rate, patient excellent response rate, lesion complete response rate in study PC T305, as compared to 79%, 83%, 85% in study PC T306.
  - In contrast to study PC T306, where all subjects had 4-10 AK lesions, only 27 (31%) and 7 (30%) subjects in Metvix and placebo, respectively, had 4-10 AK lesions at baseline in study PC T305. This might need to be reflected in the labeling even though Metvix is superior to placebo when only subjects with 4-10 AK lesions were analyzed (i.e. patient complete response rates of 67% vs. 0 for Metvix vs. placebo with p-value = 0.0075).
  - The study was conducted in Australia. It is a matter of the clinical judgement of the medical division to decide whether study PC T305 is adequate for efficacy extrapolation to the US population.

#### Supportive Trials PC T301 and PC T302

The efficacy claim of one treatment session of Metvix PDT for mild to moderate AK lesions may be supported in study PC T302, depending upon the baseline AK lesion counts considered in the labeling, as:

- 16 (84%) and 17 (94%) subjects had less than 4 AK lesions at baseline in Metvix and placebo groups, respectively. The patient complete response rates for Metvix vs. placebo are 63% vs. 12%, which are comparable to the overall patient complete response rates for the entire study (i.e. 58% vs. 11%).
- Only 3 (16%) and 1 (6%) subjects had 4-10 AK lesions at baseline in Metvix and placebo groups. The patient complete response rates are 33% vs. 0 for Metvix vs. placebo.

For study PC T301, it is difficult to assess a reliable estimate of the treatment effect for Metvix PDT treatment, as no placebo arm was included. However, it should be noted that the response rates for Metvix group in study PC T301 are comparable to those in study PC T302:

- The overall patient complete response rate, patient excellent response rate and lesion complete response rate are 47%, 55% and 69% in study PC T301, as compared to 58%, 58% and 65% in study PC T302.
- For subjects who had 1, 2, and 3 baseline AK lesions, the patient complete response rates are 80%, 45% and 33%, respectively, in study PC T301, which are comparable to those in study PC T302 (i.e. 78%, 50% and 33%).
- For subjects who had 4-10 baseline AK lesions, the patient complete response rate for Metvix treatment is 38% (= 15/40) in study PC T301, which is similar to that in study PC T302, i.e. 33% = 1/3.

It is a clinical judgement whether one treatment session of Metvix PDT therapy should be granted.

All enrolled subjects in the four Phase 3 trials are Caucasians. Whether or not Caucasian is the primary treated population for AK indication, it is a clinical issue.

From statistical point of view, studies PC T301 and PC T305 do not provide sufficient information to establish the non-inferiority claim of Metvix PDT, since:

- Placebo arm should have been included in study PC T301 to validate the efficacy results of Metvix PDT.
- The assessment was in an open-label way, which might introduce bias into efficacy evaluation.
- The choice of non-inferiority margin “15%” seems to be large, assuming the expected response rate for the active-controlled group (i.e. cryotherapy) of 90-95%.
- The non-inferiority assessment should be based on one-sided 97.5% confidence interval rather than two-sided 90% confidence interval.

Safety assessment for pivotal studies PC T305 and PC T306 based on the incidence of adverse event is:

- A higher percentage of patients had at least one adverse event in Metvix PDT group as compared to placebo arm (88% vs. 54%).
- Most adverse events in Metvix group were local adverse events. Among them, 99% of the events (i.e. 298/301) were treatment-related and most were mild to moderate in severity.
- Burning sensation skin and erythema were the most common local adverse events for Metvix and placebo PDT treatments (23%, 21% in Metvix and 18%, 27% in placebo).

Safety assessment for studies 301 and 302 based on the incidence of adverse event is:

- The adverse event incidence rates are 48% vs. 21% for Metvix vs. placebo, which are smaller than those in studies 305 and 306 (i.e. 88% vs. 54%). This could be due to the fact that a smaller number of lesions were treated and most of them (approximately 91% and 96% of lesions in studies 301 and 302, respectively) were treated with only 1 PDT session, as compared to two PDT sessions in studies 305 and 306.
- The subject discontinuation rates due to adverse events as well as serious adverse event rates are 1.6% vs. 0 for Metvix vs. placebo, which are similar to those in studies 305 and 306 (i.e. 1.5% vs. 0 for Metvix vs. placebo).

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## 2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

### 2.1. Introduction and Background

The proposed drug product, Metvix 168 mg/g Cream, is designed for a topical use in conjunction with the photodynamic therapy (PDT). According to the Sponsor, PDT is used to treat a wide variety of diseases involving skin and other organs that can be reached by light. The Sponsor indicated that the development program of the drug is due to the fact that discomfort and a non-optimal cosmetic outcome are usually associated with the conventional therapies, e.g. cryotherapy, excision and fluorouracil that are efficacious in treating actinic keratoses (AK) lesions.

Sponsor's current NDA submission claimed that one or two sessions of Metvix cream application followed by illumination with non-coherent light is effective in the treatment of mild to moderate AK lesions, located on the face or scalp. Nine clinical studies were completed and submitted in the Statistical section of the current NDA. They are:

- two Phase 3 pivotal trials (PC T305/99 and PC T306/99),
- two supportive Phase 3 trials (PC T301/99 and PC T302/99),
- one dose ranging study (PC T202/98),
- two clinical pharmacology studies (PC T107/01 and PC T108/01),
- two other supportive studies (PC T001/97 and PC T204/98).

This statistical review will primarily address the efficacy of Metvix Cream and, consequently, focus on the four Phase 3 trials (i.e. pivotal trials: PC T305/99 and PC T306/99; and supportive trials: PC T301/99 and PC T302/99). Without ambiguity, trials will be referred to as studies 305, 306, 301 and 302 throughout the review.

Table 1 presents an overview of the four Phase 3 trials. It should be noted that only study protocol 306 was submitted for the Agency's comments. There were no previous communications between the Agency and the Sponsor concerning protocols of the other three studies. Consequently, some patient inclusion criteria were different among the studies.

Two treatment arms were included in study 306. The primary objective in study 306 was to demonstrate the superiority of Metvix PDT to placebo PDT. For study 305, three treatment groups were included. The primary objectives were to show the superiority of Metvix PDT to placebo PDT, and the non-inferiority of Metvix PDT to cryotherapy. Study 302 included treatment arms of Metvix PDT and placebo PDT and the primary objective was to demonstrate the superiority of Metvix PDT to placebo PDT. For study 301, Metvix PDT and cryotherapy were included. The primary objective was to show the non-inferiority of Metvix PDT to cryotherapy.

It should be noted that the treatment procedures of Metvix PDT and cryotherapy in studies 301 and 302 differ from those in pivotal trials 305 and 306. This might have impact on the efficacy results:

- In studies 301 and 302, only 1 session of PDT (i.e. Metvix or placebo) was performed for lesions located on the face or scalp. This was different from those in studies 305 and 306, where two treatment sessions with 7 days apart were applied to lesions on the face or scalp.

- For study 301, two freezing cycles were applied to lesions in cryotherapy group. This was different from the cryotherapy treatment in study 305, where only 1 freezing cycle was performed.

**Table 1. Overview of the Four Phase 3 Trials**

Study	Study conducted	Patients inclusion	Treatment arms, n	Comments on treatments
<b>Pivotal Trials</b>				
306	US (6/00-2/01)	4-10 mild to moderate AK lesions on the face or scalp	Metvix PDT: 42 Placebo PDT: 38	Patients were treated with two treatment sessions with 7 days apart
305	Australia (3/00-12/00)	Unlimited mild to moderate AK lesions on the face or scalp	Metvix PDT: 91 Placebo PDT: 23 Cryotherapy: 90	<u>PDT</u> : two sessions with 7 days apart <u>Cryotherapy</u> : one treatment session with one freezing cycle
<b>Supportive Trials</b>				
302	Europe (6/99-1/00)	1-10, any grades of AK lesions located on any locations	Metvix PDT: 20 Placebo PDT: 19	<u>PDT</u> : only <u>one</u> session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations
301	Europe (4/99-11/99)	1-10, any grades of AK lesions located on any locations, suitable for cryotherapy	Metvix PDT: 102 Cryotherapy: 100	<u>PDT</u> : only <u>one</u> session applied to lesions on the face or scalp; two sessions with 7 days apart were for lesions on other locations. <u>Cryotherapy</u> : one treatment session with two freezing cycles

**Reviewer's Comments:**

It should be noted that, from statistical point of view, results from studies 301 and 305 do not have sufficient information to establish the non-inferiority assessment between Metvix PDT and cryotherapy since:

- Study 301 did not include a placebo arm. It is difficult to get a reliable estimate of treatment effect for Metvix PDT without placebo arm.
- The assessment was in an open-label way, which might introduce bias into efficacy evaluation (refer to ICH E9 Guidance).
- The choice of non-inferiority margin "15%" in the studies may seem to be large, assuming the expected patient excellent response rate in cryotherapy group of 90-95%.

Following a discussion with the clinical reviewer, only the superiority evaluation of Metvix PDT to placebo PDT is of interest in this NDA. Therefore, this statistical review will focus on the superiority evaluation. The non-inferiority assessment is not reported. However, descriptive efficacy results will be presented.

**2.2 Data Analyzed and Sources**

The data summary in this review is based on the Sponsor's NDA submission as well as electronic SAS data sets submitted on 9/26/01, 12/13/01, 12/19/01, 4/19/02 and 5/6/02.

## **2.3 Statistical Evaluation of Evidence on Efficacy/Safety**

Results of the efficacy and safety for studies 305 and 306 are evaluated in this section.

### **2.3.1. Efficacy Review of Studies 305 and 306**

#### **Study Design**

Study 305 was designed as randomized, 3-arm, parallel-group and multicenter (i.e. 9 centers), and was conducted in Australia during March 2000 – December 2000. The objectives were to show the superiority of Metvix PDT to placebo PDT, and non-inferiority of Metvix PDT with respect to cryotherapy in the treatment of AK lesions.

A total of 204 patients, who were above 18 years of age and had unlimited number of mild to moderate AK lesions on the face or scalp, were enrolled and randomized to Metvix PDT, cryotherapy and placebo PDT treatments. This resulted in 91, 90 and 23 patients in the three treatment groups, respectively. However, only 88, 89 and 23 patients were treated with the corresponding treatment. The details about the randomization/blinding are presented in Appendix A.

The PDT therapy included 2 treatment sessions with a period of 7-day apart. At each session, the assigned cream (i.e. either Metvix or placebo) was applied to AK lesions for 3 hours followed by the illumination of red light (570-670 nm) with fluency of 75 J/cm<sup>2</sup>. The clinical assessment of lesion response was at the 3-month post-treatment.

Study 306 was designed as randomized, double-blind, placebo-controlled, parallel-group and multicenter (i.e. 5 centers) conducted in US during June 2000 – February 2001. The objective of the study was to demonstrate the superiority of Metvix PDT to placebo PDT in the treatment of AK lesions. Subjects of greater than 18 years of age who had 4-10 mild to moderate AK lesions on the face or scalp and satisfied the inclusion criteria were enrolled. A total of 80 enrolled subjects were randomized in an equal allocation to Metvix PDT and placebo PDT treatments. This resulted in 42 and 38 patients, respectively. The details of randomization/blinding procedure are presented in Appendix A.

Similar to study 305, the PDT therapy in study 306 included 2 treatment sessions that were 7 days apart. The cream application time at each session was approximately 3 hours followed by illumination procedure. The lesion response was evaluated at the 3-month post-treatment.

#### **Efficacy Endpoints Specified in the Protocol and Amendments:**

##### **▪ Study 305:**

Sponsor's efficacy endpoints specified in the protocol and amendments were the following:

- **Primary:** Patient's weighted mean lesion response
- **Secondary:**
  - ✓ Patient complete response rate
  - ✓ Lesion complete response rate across patients
  - ✓ Cosmetic outcome evaluated by investigators and patients for patients who had complete response of all lesions

It should be noted that the primary efficacy endpoint was changed from “patient’s excellent response rate” during the course of the trial; while “patient complete response rate” was added as one of the secondary efficacy endpoints (per protocol amendment #2 dated 6/6/00). Sponsor’s sample size/power calculation was based on the patient excellent response rate prior to initiation of the trial.

▪ Study 306:

The therapeutic effectiveness of Metvix PDT over placebo PDT was evaluated at the 3-month post-treatment based on the following efficacy endpoints specified in the protocol:

- Primary: percentage of subjects with complete response of all lesions.
- Secondary:
  - ✓ Lesion complete response rate across patients
  - ✓ Patient’s weighted mean lesion response
  - ✓ Cosmetic outcome evaluated by investigators and patients for subjects who had complete response of all lesions

For the evaluation of lesion response at the 3-month post-treatment, the response of each lesion was rated either

- CR = complete response – complete disappearance of lesions, or
- Non-CR = non-complete response – incomplete disappearance of lesions

Patient complete response rate was defined as the percentage of subjects who had 100% of all lesions cleared. Patient’s excellent response rate was defined as the percentage of subjects with disappearance of 75%-100% of all lesions. For patient’s weighted mean lesion response, the computation, according to the Sponsor, takes into account the baseline AK lesion counts per patient. The details are presented in Appendix B.

For the assessment of cosmetic outcome, a 4-point scale was used, and only patients with complete response for all lesions at 3-month post-treatment were evaluated:

- Excellent = No scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared to adjacent skin.
- Good = No scarring, atrophy or induration but moderate redness or change in pigmentation compared to adjacent skin.
- Fair = Slight to moderate occurrence of scarring, atrophy or induration.
- Poor = Extensive occurrence of scarring, atrophy or induration.

Population Analyzed in the Protocol/Submission:

Two populations were analyzed in the Sponsor’s protocol and submission:

- Intent-to-treat (ITT) population: defined as all patients who were randomized and treated. Their primary analysis was based on such population.
- Per-Protocol (PP) population included subjects who completed study and did not have substantial protocol deviation.

The details of inclusion/exclusion in the ITT and PP populations are presented in Table 2. For handling missing values in lesion evaluation, they were treated as non-complete responders in both populations.

Statistical Analysis Plan in the Protocol:

- Cochran-Mantel-Haenszel test adjusting for study center was proposed to analyze the patient complete response rate in study 306. Fisher's exact test was proposed in the original protocol (dated 10/29/1999) to analyze the patient's excellent response rate in study 305.
- Analysis of variance (ANOVA) was proposed to analyze the patient's weighted mean lesion response. The model included terms for treatment, center, and center-by-treatment interaction, where the interaction was tested at a 10% significance level.
- Descriptive statistics was applied to other efficacy endpoints.

Comparison Criteria:

The primary comparison was Metvix PDT against placebo PDT. The criterion for superiority evaluation was that p-value < 0.05.

Multiplicity Issues:

No multiplicity adjustment is needed as one primary efficacy endpoint was specified in the protocols.

*Reviewer's Comments on Studies 305 and 306:*

1. Study 305 was conducted in Australia, and has not previously been communicated to the Agency. The following are issues and comments for study 305:
  - For extrapolation of efficacy results of a trial conducted in a foreign county, a clinical judgement is required.
  - Study 305 enrolled patients with unlimited number of mild to moderate AK lesions, located on the face or scalp. This is in contrast to study 306, where patients with 4-10 lesions were enrolled. This might have an impact on the labeling claim.
  - The blinding might be an issue, as the investigators rather than other party handled the illumination procedure as well as recording of local adverse events. Consequently, bias might be introduced into efficacy evaluation, as the local adverse events for Metvix group occurred more frequently than placebo during illumination.
  - The primary efficacy endpoint was patient excellent response rate in the original protocol (dated 10/29/1999). However, it was replaced by patient's weighted mean lesion response, and patient complete response rate was added as one of the secondary efficacy endpoints during the course of the trial (per pages 245-246, Volume 45, for protocol amendment #2 dated 6/6/2000).
2. According to the Sponsor, the center in Austin, Texas was added into trial 306 (per pages 217-218, Volume 42, for protocol amendment #4 dated 8/22/00) due to slow enrollments in the other 4 centers. The 1<sup>st</sup> patient enrollment in the center was 9/28/00. This will be commented in the efficacy review section.
3. As commented by the Agency at the Pre-IND/End-of-Phase 2 meeting (dated 6/22/2000):
  - The primary efficacy endpoint is the percentage of patients who achieve 100% clearance of all lesions 3 months after treatment (i.e. patient complete response rate). The percentage of patients who achieve 75-100% clearance of lesions 3 months after treatment (i.e. patient excellent response rate) could be a secondary efficacy endpoint.
  - The lesion complete response rate across patients is algebraically the same as the patient's weighted mean lesion response (per Appendix B for illustration) and has the advantage of being readily comprehensible to patients and practitioners.

Consequently, following a discussion with the clinical reviewer, the efficacy endpoints included in this review are:

- **Primary:** Patient complete response rate at 3-month post-treatment
- **Secondary:**
  - Patient excellent response rate at 3-month post-treatment
  - Lesion complete response rate 3 months after treatment.

Results of other efficacy endpoints are not reported.

4. Sponsor's ITT population, which included all randomized patients who were treated, is acceptable, as compared to the Division's recommendation on ITT population – all randomized subjects who are dispensed drug medication since:
  - The difference between the randomized and treated subjects is small, and, consequently, does not have impact on the efficacy results.
  - The trials were not outpatient practice, as the patients who were dispensed drug medication in the studies underwent the assigned treatment at centers the same day.

**Efficacy Results for Studies 305 and 306:**

**1. Patient Disposition and Baseline Characteristics**

To evaluate the comparability between treatments, Table 2 presents the patient disposition for studies 305 and 306. Generally, the discontinuation rate was small and comparable between treatment groups within each study. Treatment groups were comparable with respect to the ITT, PP populations as well as subjects who completed studies within each trial. For the treatment distribution by center, the results are presented in Table CIII.1 of the Appendix.

**Table 2. Patient Disposition, n (%): Studies 305 and 306**

	Study 305			Study 306	
	Metvix	Cryotherapy	Placebo	Metvix	Placebo
<b>Randomized</b>	91	90	23	42	38
<b>Treated (ITT population)</b>	88 (97%)	89 (99%)	23 (100%)	42 (100%)	38 (100%)
<b>Completed study</b>	87 (96%)	87 (97%)	23 (100%)	40 (95%)	38 (100%)
<b>Discontinued</b>	4 (4.4%)	3 (3.3%)	0	2 (5%)	0
Consent withdrawn	1	1	0	0	0
Adverse event	1	0	0	1 (2.4%)	0
Lost to follow-up	1	2	0	1 (2.4%)	0
Other	1	0	0	0	0
<b>Protocol deviation</b>	10 (11%)	1 (1.1%)	4 (17%)	1 (2.4%)	0
<b>Per-Protocol population</b>	77 (85%)	86 (96%)	19 (83%)	39 (93%)	38 (100%)

Source: Sponsor's NDA submission (pages 32 and 64, Volume 42; pages 69-70, Volume 45)

For the comparison between treatments with respect to demographics and baseline characteristics, Table CIII.2 of the Appendix summarizes the results. Generally, no outstanding discrepancies between treatments are identified within each study. However, a difference between Metvix and placebo in the baseline lesion severity rates within study is observed (i.e. p-

value = 0.0368 in study 306, and p-value = 0.0897 in study 305). Metvix group had a higher rate of mild lesions within each study. This issue will be discussed in the efficacy review section.

More than 60% of enrolled subjects in study 305 had less than 4 AK lesions at baseline. This is in contrast to that in study 306, where only subjects with 4-10 AK lesions were enrolled. Further comparisons will be discussed in the efficacy review section.

It should be noted that all subjects enrolled are Caucasians in both studies. Whether Caucasian is the primary population for this indication, clinical reviewer should comment on this issue.

## 2. Primary Efficacy Endpoint

### Overall Analysis:

Efficacy results in the percentage of subjects who had 100% clearance of all lesions 3 months post-treatment for studies 305 and 306 are presented in Table 3.

**Table 3: Subjects with 100% of Lesions Cleared 3-Month Post-Treatment**

<b>SUTDY 305</b>	<b>Metvix (n=88)</b>	<b>Placebo (n=23)</b>	<b>Cryotherapy (n=89)</b>	<b>p-value<sup>1</sup></b>
<b>ITT analysis n (%)</b>	71 (81%)	3 (13%)	51 (57%)	< 0.001
<b>PP analysis n/N (%)</b>	63/77 (82%)	2/19 (11%)	51/86 (59%)	< 0.001
<b>STUDY 306</b>	<b>Metvix (n=42)</b>	<b>Placebo (n=38)</b>		<b>p-value<sup>1</sup></b>
<b>ITT analysis n (%)</b>	33 (79%)	8 (21%)		< 0.001
<b>PP analysis n/N (%)</b>	32/39 (82%)	8/38 (21%)		< 0.001
Source: Sponsor's NDA submission (pages 78-81, Volume 42; pages 87-88, Volume 45)				
<sup>1</sup> p-value is the comparison between Metvix and Placebo groups, and is based on Cochran-Mantel-Haenszel test adjusting for center.				

The summary of Table 3 is:

- Analyses based on ITT and PP populations are consistent.
- Metvix PDT is superior to placebo PDT as p-value < 0.001 in both studies.

As commented previously, the center in Austin was added during the course of trial 306 (i.e. amendment was dated 8/22/00 and 1<sup>st</sup> patient was enrolled on 9/28/00). This study center accounts for 15% of the enrolled subjects (i.e. 12/80 = 15%). However, this does not have impact on the overall efficacy results as:

- The patient complete response rates in the center are 83% vs. 17% for Metvix vs. placebo, which are similar to those at the other centers.

### Subgroup Analysis:

An issue was raised previously that more than 60% of enrolled subjects in study 305 had less than 4 AK lesions at baseline. To investigate the impact of baseline lesion counts on the patient complete lesion response rate, subgroup analysis of patient complete response rate by baseline lesion counts is performed and the results are presented in Tables CIII.3 (a)-(b) of the Appendix:

- Metvix cream is better than placebo in patient complete response rate for each lesion number category. The patient complete response rate generally decreases as patients' baseline lesion number increases.
- In study 305, only 27 and 7 patients in Metvix and placebo groups (i.e. 31% and 30%), respectively, had 4-10 AK lesions at baseline. Metvix PDT is superior to placebo PDT in the patient complete response rate even when only subjects with 4-10 AK lesions were analyzed (i.e. response rates of 67% vs. 0 for Metvix vs. placebo with p-value = 0.0075).

Subgroup efficacy results by gender and age are examined. The treatment effect of Metvix PDT was generally similar across subgroups. No significant disparity among subgroups is indicated. The efficacy of Metvix PDT is superior to placebo PDT in each gender of study 305, male group in study 306, and each of age groups in both studies (p-value < 0.001). Metvix PDT is numerically better than placebo PDT, but not statistically, for female subjects in study 306. The non-statistically significant result is due to small sizes of females enrolled (6/42 = 14%, and 4/38 = 11% for Metvix and placebo).

The efficacy results for patient complete response rate by center are presented in Table CIII.4 of the Appendix. Generally, no outstanding differences are indicated across centers within each study. For study 305, the patient complete response rate in Metvix group may be relatively low for the center in — is compared to other centers; while the response rate in placebo was high for the center in Adelaide (Dr. Reid) as compared to others. However, the definite conclusion could not be drawn due to small sizes.

### 3. Secondary Efficacy Endpoints

The secondary efficacy endpoints evaluated at 3 months after treatments included:

- Percentage of subjects with excellent lesion response
- Lesion complete response rate across patients

For the comparison of patient excellent response rate, the efficacy results of the two studies are presented in Table 4. Both studies showed that Metvix PDT is significantly more effective than placebo PDT (p-value < 0.001).

**Table 4: Percentage of Subjects with 75-100% Clearance of Lesions at the 3-Month Post-treatment (Reviewer's Analysis)**

SUTDY 305	Metvix (n=88)	Placebo (n=23)	Cryotherapy (n=89)	p-value <sup>1</sup>
ITT analysis n (%)	76 (86%)	4 (17%)	61 (69%)	< 0.001
PP analysis n/N (%)	68/77 (88%)	3/19 (16%)	61/86 (71%)	< 0.001
STUDY 306	Metvix (n=42)	Placebo (n=38)		p-value <sup>1</sup>
ITT analysis n (%)	35 (83%)	12 (32%)		< 0.001
PP analysis n/N (%)	34/39 (87%)	12/38 (32%)		< 0.001

Source: Sponsor's submission dated 12/19/01.  
<sup>1</sup> p-value is the comparison between Metvix and Placebo groups, and is reviewer's analysis based on Cochran-Mantel-Haenszel test adjusting for center.

For subgroup analysis, results of patient's excellent lesion response rate by baseline lesion counts are presented in Table CIII.5 of the Appendix. The results show that Metvix PDT is better than placebo PDT over each baseline lesion number category. The subgroup analysis by gender and age generally shows that Metvix PDT is more effective than placebo PDT. No significant discrepancies are indicated.

For the comparison in lesion complete response rate across patients, the results are presented in Table 5:

- Results of ITT and PP analyses are consistent
- Metvix PDT is superior to placebo PDT (p-value < 0.001 in both studies based on Cochran-Mantel-Haenszel test adjusting for study center).

**Table 5: Lesion Complete Response Rate at the 3-Month Post-treatment**

<b>SUTDY 305</b>	<b>Metvix (c=360)</b>	<b>Placebo (c=74)</b>	<b>Cryotherapy (c=421)</b>
<b>ITT analysis n (%)</b>	317 (88%)	21 (28%)	283 (67%)
<b>PP analysis n/N (%)</b>	267/295 (91%)	18/61 (30%)	278/407 (68%)
<b>STUDY 306</b>	<b>Metvix (c=260)</b>	<b>Placebo (c=242)</b>	
<b>ITT analysis n (%)</b>	221 (85%)	92 (38%)	
<b>PP analysis n/N (%)</b>	209/236 (89%)	92/241 (38%)	
Source: Summary is based on the Sponsor's NDA submission (pages 88-89, Volume 42; pages 82-83, Volume 45).			

Discussion:

As indicated previously that Metvix groups had higher percentages of mild lesions at baseline than placebo group within each study, subgroup analysis by baseline lesion severity as well as lesion location is examined. The results are presented in Tables CIII.6-7 of the Appendix. The summary is:

- Metvix is better than placebo in lesion complete response rate regardless of lesion severity and lesion location.
- Lesion complete response rate is numerically higher for mild (or thin) lesions than for moderate lesions. The response rate was approximately 90% for mild lesions and about 78% for moderate lesions in Metvix groups.
- Most lesions were located on the face (about 82%). The lesion complete response rate was about 89% for lesions on the face, and about 76% for lesions on the scalp in Metvix groups.

4. Discontinuation and Missing Values Handling

For each of studies 305 and 306, the discontinuation rate ranged between 0 and 5.0% over treatment groups (per Table 2). The treatment arms were comparable within each study in terms of study completion rate. Consequently, patient discontinuation is not expected to have a significant impact on the efficacy results.

Sponsor's ITT analysis treated missing lesion response data as failures in both Metvix and placebo groups. This reviewer performed an analysis based on the worst case scenario (i.e. treat missing data as failures in Metvix group and successes in placebo group) to evaluate the impact on the ways of handling missing values. The results are presented in Table CIII.8 of the Appendix. No significant discrepancies are indicated.

#### 5. The Effect of Illumination Procedure

It should be noted that the cream application (i.e. Metvix or placebo) must be followed by illumination. Consequently, data of illumination time, light dose, light intensity, light field diameter and cream application time are examined.

##### Within Study:

Generally, the illumination time, light dose, light intensity, light field diameter and cream application time were comparable between Metvix and placebo groups within each study center at each of two PDT treatment sessions except the center in Adelaide (Dr. Reid) in study 305. The average illumination time was 11 minutes vs. 7.3 minutes for Metvix vs. placebo in the center of Adelaide (Dr. Reid). The patient complete response rates are 67% vs. 67% for Metvix vs. placebo. However, formal statistical testing for the difference is not appropriate because of small sample sizes (i.e. 6 in Metvix and 3 in placebo).

It should be noted that the centers in \_\_\_\_\_ and Liverpool in study 305 had relatively longer average illumination time than other centers (i.e. 13 minutes vs. 10 minutes for other centers). However, these centers did not result in the extreme patient complete response rates. Therefore, it can be concluded that no outstanding discrepancy is indicated for the illumination procedure between Metvix PDT and placebo PDT within each study.

##### Between Study:

The results in illumination time, light dose, light intensity, light field diameter and cream application time for each study are summarized in Table CIII.9 of the Appendix. The results presented are based on two treatment sessions combined for each study.

Note that study 305 had longer mean illumination times and larger mean light field diameters, however, had lower mean light dose and mean light intensity than those in study 306 (per Table CIII.9 of the Appendix). The average cream application times were generally similar between studies. From statistical point of view, the impact of these factors on the efficacy results is not pronounced, as the efficacy results were similar between studies. Whether or not the length of cream application time and illumination procedure is appropriate, the clinical and device reviewers should comment on this issue.

#### **2.3.2 Safety Review of Studies 305 and 306**

Safety assessment of Metvix and placebo based on the incidence rates of adverse events, serious adverse events and withdrawals due to adverse events is summarized in Table 6. Results of local adverse events occurred in the therapy of PDT are presented in Table 7. The results presented are based on studies 305 and 306 combined.

**Table 6: Overall Incidence of Adverse Events: Studies 305 and 306 Combined**

Events	Metvix PDT (n=130)	Placebo PDT (n=61)	Cryotherapy (n=89)
Subjects with at least one adverse event	114 (88%)	33 (54%)	43 (48%)
Total adverse events	488	76	89
Total local adverse events	301	44	49
Local adverse events by intensity:			
Mild: total events	149	38	36
Moderate: total events	123	6	7
Severe: total events	29	0	6
Total treatment-related local AEs	298	41	46
Adverse events by intensity:			
Mild: total events	146	36	33
Moderate: total events	123	5	7
Severe: total events	29	0	6
Subjects with adverse events resulting in discontinuation	2 (1.5%)	0	0
Serious adverse events	2 (1.5%)	0	0
Deaths	0	0	0
Source: Sponsor's NDA submission (pages 50-52, Volume 42; pages 55-58, Volume 45).			

**Table 7: Summary of Local Adverse Events**

Events	Metvix PDT (n=130)	Placebo PDT (n=61)
Subjects with at least one adverse event	114 (88%)	33 (54%)
Total adverse events	488	76
Total local adverse events	301	44
# of local adverse events:		
Burning sensation skin	70 (23%)	8 (18%)
Erythema	64 (21%)	12 (27%)
Crusting	20 (7%)	6 (14%)
Pain skin	29 (10%)	3 (7%)
Blisters	14 (5%)	2 (5%)
Oedema skin	21 (7%)	1 (2%)
Stinging skin	25 (8%)	2 (5%)
Skin ulceration	7 (2%)	0
Skin peeling	14 (5%)	2 (5%)
Pruritus	8 (3%)	2 (5%)
Itching	9 (3%)	0
Bleeding skin	11 (4%)	2 (5%)
Irritability skin	1 (< 0.5%)	0
Milia	1 (< 0.5%)	0
Hyperkeratosis	0	1 (2%)
Skin infection	3 (1%)	1 (2%)
Dermatitis contact	1 (< 0.5%)	0
Photosensitivity toxic reaction	1 (< 0.5%)	0
Rosacea	1 (< 0.5%)	0
Skin hyperpigmentation	1 (< 0.5%)	0
Skin disorder	0	1 (2%)
Skin inflammatory NOS	0	1 (2%)
Source: Sponsor's NDA submission (pages 97-99, Volume 42; pages 57-58, Volume 45).		

Results from Tables 6-7 are summarized below:

- A higher percentage of patients had at least one adverse event in Metvix PDT group as compared with placebo arm (88% vs. 54%, Table 6).
- Most adverse events in Metvix group were local adverse events. Among them, 99% of the events (i.e. 298/301) were treatment-related and most were mild to moderate in severity. Two subjects (1.5%) in Metvix group discontinued the treatment due to adverse events (Table 6).
- Burning sensation skin and erythema were the most common local adverse events for Metvix and placebo PDT (23%, 21% in Metvix and 18%, 27% in placebo, Table 7).

## 2.4 Findings in Special/Subgroup Populations

No significant discrepancies in efficacy results are indicated over subgroup for studies 305 and 306 (see Section 2.3.1 for details).

## 2.5 Statistical and Technical Issues

Following a discussion with the clinical reviewer, blinding might be an issue for studies 305 and 306, where the severity is in a different degree (refer to Appendix A for details).

Even though study nurses administered illumination procedure and recording of local adverse events in study 306, however, investigators might be able to differentiate the treatment assignments at the visit of the 2<sup>nd</sup> treatment session. This is because that two PDT treatment sessions were only 7 days apart and safety measures (i.e. crusting, blisters, erythema and burning sensation skin) resulted from the 1<sup>st</sup> session might not be well resolved by the time of the 2<sup>nd</sup> treatment session. In study 305, investigators administered illumination procedure as well as recording of local adverse events. This might introduce a different degree of bias, if any, into efficacy evaluation. Therefore, it would be difficult to assess the magnitude of bias for study 305, if any, as compared to study 306. This will be commented in the section of conclusions and recommendations.

To investigate the possible unblinding in study 306, the safety data – duration of the adverse events (i.e. crusting, blisters, erythema, and burning sensation skin), start and stop dates, as well as PDT treatment session dates, are examined.

The blinding is not an issue for the event of burning sensation skin, as the duration of all cases was fairly short and resolved within few days (most were within the same day).

For the events of crusting and blisters, there were about 10 patients, including 1 in placebo and 9 in Metvix, that investigators might be able to observe these events at the visit of 2<sup>nd</sup> treatment sessions (i.e. patient IDs: 2005, 2019, 2021, 2024, 4010, 4015, 5001, 5002, 5007 and 5010).

Thirty subjects had the event of erythema, including 22 and 8 patients in Metvix and placebo, respectively. Among them, 21 and 3 subjects in the respective group had 100% of all lesions cleared 3 months after treatment. Since the duration of erythema was rather long as compared to other events, 14 and 2 subjects in Metvix and placebo arm who had 100% lesions cleared had erythema event duration overlapping the 2<sup>nd</sup> PDT treatment session date.

It should be noted that all events were resolved by the time of lesion evaluation (i.e. 3-month post-treatment). Following a discussion with the clinical reviewer, a sensitivity analysis is performed. The subjects referred above in possible unblinding situations are imputed as failures in the analysis. The result demonstrates that Metvix PDT is better than placebo PDT in terms of patient complete response rates (i.e. 36% (15/42) vs. 16% (6/38) for Metvix vs. placebo with a p-value of 0.0474).

## **2.6 Evaluation of Collective Evidence**

Two Phase 3 study results (studies 301 and 302) are submitted to support Metvix drug application. Both studies were conducted in Europe. This section evaluates the efficacy of Metvix PDT treatment.

### **2.6.1 Efficacy Evaluation for Study 302.**

#### **Study Design and Endpoints**

Study 302 was conducted during June 1999 – January 2000. It was designed as randomized, double-blind, placebo-controlled, and multicenter (i.e. 4 centers). According to the Sponsor, 39 patients were enrolled and randomized into two treatment groups, which resulted in 20 subjects in Metvix PDT and 19 subjects in placebo PDT. More details about the randomization are included in Appendix D.

According to the Sponsor, the enrolled patients had 1-10 any grades of AK lesions, located on any locations (about 94% and 100% of AK lesions were on the face or scalp for Metvix and placebo, respectively). The primary objective was to demonstrate the superiority of Metvix to placebo in patient excellent response rate 3 months after treatment. It should be noted that lesions located on the face or scalp were treated with only one PDT session in the study; while others (i.e. lesions located on trunk or extremities) were applied two PDT sessions with 7 days apart. The assessment of lesion response was at the 3-month post-treatment.

The primary efficacy endpoint pre-specified in the protocol was the percentage of patients with excellent lesion response. The secondary efficacy endpoints included lesion complete response rate, and cosmetic outcome.

Sponsor's analysis for the efficacy endpoints was based on a two-sided 95% confidence interval. That is, the superiority of Metvix to placebo was demonstrated if limits of the 95% confidence interval for the percentages difference (i.e. Metvix – placebo) were positive.

The population analyzed for efficacy included patients who were randomized and completed the study. This included 19 and 18 patients in Metvix and placebo groups, respectively.

#### **Reviewer's Comments on Study 302:**

1. As the Sponsor's labeling claims that —  
— however, blinding might be an issue for study 302:

- Investigators administered the illumination procedure. According to the Sponsor, the patients randomized to Metvix might have experienced pain or burning sensation. The blinding was therefore not optimal after the time of illumination procedure (per page 20, Volume 49).
  - The Sponsor's protocol amendment #2 (dated 7/7/1999, page 30, Volume 49) indicated that Metvix and placebo creams had been filled in tubes with different caps. Their on-site randomization procedure was terminated and replaced by a central randomization procedure. However, fourteen patients (i.e. 6 and 8 patients in Metvix and placebo, respectively) were enrolled by this time.
  - The Sponsor claimed that a blinded assessment of the lesion response based on photographic documentation was added in the amendment #2 of the protocol. The Sponsor, however, did not include results of this assessment (page 30, Volume 49) in the submission.
2. Efficacy results from study 302 will be summarized in this review. The result of patient complete response rate is also presented, as this is the primary efficacy endpoint recommended by the Agency for pivotal trials.

### Efficacy Results for Study 302:

#### 1. Patient Disposition and Baseline Characteristics

A total of 39 patients were enrolled and randomized to Metvix (20 subjects) and placebo (19 subjects). Of these, one subject (5%) randomized in Metvix withdrew without receiving any treatment; while one subject (5%) in placebo group withdrew before the lesion response evaluation. All other patients completed the study (i.e. 19 patients in Metvix and 18 in placebo). No discrepancy between treatments is noted in terms of patient discontinuation rate, and populations analyzed for efficacy.

Of the 20 patients in Metvix group, 16 are males (80%). Of the 19 subjects in placebo arm, only 9 (47%) are males. The age of the enrolled subjects ranged from 43 to 87 years. The mean age was 67 years in Metvix and 69 in placebo.

For the subjects who completed the trial, about 84% (=16/19) and 94% (=17/18) of subjects had 1-3 AK lesions at baseline in Metvix and placebo, respectively. Among them, 47% (=9/19) and 44% (=8/18) of subjects in Metvix and placebo, respectively, had 1 AK lesion. Approximately 92% (=45/49) and 94% (34/36) of AK lesions in the respective group were mild to moderate in severity at baseline. Also, the majority of lesions were located on the face or scalp (about 94% and 100% in Metvix and placebo, respectively).

#### 2. Efficacy Results

The efficacy endpoints of interest (from the protocol) at 3 months after treatment are:

- Primary: Percentage of patients with excellent lesion response
- Secondary: Lesion complete response rate

Result of the patient complete response rate is also included in the review, as it was recommended by the Agency as the primary efficacy endpoint in the pivotal trial. Results are presented in Table 8. Metvix PDT is better than placebo PDT with respect to each of the efficacy endpoints listed (p-value < 0.001).

**Table 8: Efficacy Results for Study 302**

Efficacy endpoint	Metvix (n=19)	Placebo (n=18)	Comparison	
			Sponsor <sup>1</sup>	Reviewer <sup>3</sup>
Percent of patients with 100% of lesions cleared	11 (58%)	2 (11%)	N/A	< 0.001
Percent of patients with excellent lesion response	11 (58%)	2 (11%)	(20%, 73%)	< 0.001
Lesion complete response rate <sup>2</sup>	32/49 (65%)	6/36 (17%)	N/A	< 0.001

Source: Sponsor's NDA submission (pages 35-38, 55, Volume 49).  
<sup>1</sup> Sponsor's results are based on 95% confidence interval for the difference (i.e. Metvix – placebo).  
<sup>2</sup> Calculation is based on the number of lesions treated.  
<sup>3</sup> p-value is based on Cochran-Mantel-Haenszel test adjusting for site.

Results of patient complete lesion response rate by baseline lesion counts are presented in Table 9. Efficacy results of the lesion complete response rate by baseline lesion severity as well as by lesion location are summarized in Table CIII.10 of the Appendix. The summary of Table 9 is:

- Metvix PDT is numerically better than placebo PDT over each of baseline lesion counts.
- 16 (84%) and 17 (94%) subjects had less than 4 AK lesions at baseline in Metvix and placebo groups, respectively. The patient complete response rates for Metvix vs. placebo are 63% vs. 12% for subjects having 1-3 AK lesions, which are similar to the overall patient complete response rates for the entire study (i.e. 58% vs. 11%).
- Only 3 (16%) and 1 (6%) subjects had 4-10 AK lesions at baseline in Metvix and placebo groups. The patient complete response rates are 33% vs. 0 for Metvix vs. placebo.

**Table 9: Patient Complete Lesion Response Rates by Baseline AK Counts: Study 302**

Study 302	Number of Lesions per Patient							Total
	1	2	3	4	5	9	10	
Metvix (n=19)	7/9 (78%)	2/4 (50%)	1/3 (33%)	0/1	--	1/1 (100%)	0/1	11/19 (58%)
Placebo (n=18)	2/8 (25%)	0/4	0/5	--	0/1	--	--	2/18 (11%)
p-value *								< 0.001

Source: Summary is based on the Sponsor's electronic SAS data sets (files: les\_.xpt, pdt\_.xpt, and demo.xpt).  
 \* p-value is based on Cochran-Mantel-Haenszel test adjusting for study site.

The summary of Table CIII.10 of the Appendix is:

- Metvix PDT is numerically better than placebo PDT regardless of lesion severity and lesion location.

As indicated in the reviewer's comments that Metvix and placebo creams had been filled in tubes with different caps till amendment #2 of the protocol issued on 7/7/99, this might have an implication of possible unblinding. Fourteen patients were enrolled at Center 1 (i.e. Investigator —), by the date of 7/7/99. Six and 8 patients were in Metvix and placebo group, respectively. Response rates of the 14 subjects were examined to investigate the impact of the possible unblinding on the efficacy results. The summary is:

- The patient complete response rates for Metvix vs. placebo based on the 14 subjects are 6/6 (= 100%) vs. 1/8 (= 12.5%). This is similar to the overall response rates for Center 1, i.e. 7/8 (=87.5%) vs. 1/11 (= 9%). However, the response rates might seem to be relatively large as compared to the overall response rates for the entire study as well as each of the other centers (i.e. overall: 11/19 (= 58%) vs. 2/18 (= 11%); 0/2 vs. 0/0 at Center 2; 0/3 vs. 0/2 at Center 3; and 4/6 (=67%) vs. 1/5 (=20%) at Center 4). This might have the implication that the overall efficacy result is driven by Center 1.
- To investigate the implication that efficacy results are driven by Center 1, sensitivity analysis is performed by imputing the 14 subjects who enrolled prior to 7/7/99 at Center 1 as failures. This results in patient complete response rates of 5/19 (= 26.3%) vs. 1/18 (= 6%) for Metvix vs. placebo (p-value = 0.0624). The analysis shows that Metvix is superior to placebo.

## **2.6.2 Efficacy Evaluation for Study 301**

### **Study Design and Endpoints**

Study 301 was designed as a randomized, open-label, active-controlled, and multicenter (i.e. 13 centers) trial conducted during April 1999 – November 1999. Two hundred and two patients, who were more than 18 years of age and had one or more any grades of AK lesions located on any locations, were enrolled and randomized into Metvix PDT and cryotherapy. This resulted in 102 and 100 patients in the respective treatment group. The primary objective was to demonstrate that Metvix PDT is non-inferior to cryotherapy with respect to patient excellent response rate. It should be noted that only 1 Metvix PDT session was performed on the lesions located on the face or scalp in the study.

The primary and the secondary efficacy endpoints specified in the study protocol included:

- Primary: percentage of patients with excellent lesion response
- Secondary:
  - Lesion complete response rate across patients
  - Cosmetic outcome evaluated by investigator and patient for patients who had excellent lesion response
  - Patient's satisfaction

The efficacy evaluation time point was 3 months after treatment.

A two-sided 90% confidence interval for the difference between treatments (i.e. cryotherapy – Metvix) along with a non-inferiority margin of 15% were used for non-inferiority efficacy assessment. The Sponsor claimed the non-inferiority of Metvix PDT to cryotherapy if the upper limit of the confidence interval was no more than 15%.

For efficacy assessment, the Sponsor's primary analysis excluded patients who did not have 3-month post-treatment lesion response data. This resulted in 98 and 95 patients in Metvix PDT and cryotherapy treatments, respectively. The per-protocol analysis was also performed, which included 97 and 94 patients in the respective group.

### **Reviewer's Comments on Study 301:**

1. From statistical point of view, it is difficult to make efficacy claim from study 301 since

- The trial did not include a placebo arm. It is difficult to get a reliable estimate of treatment effect for Metvix PDT without placebo arm. Consequently, with this study design, the efficacy claim for Metvix PDT with respect to placebo cannot be concluded.
  - It was an open-label study, which might introduce bias into efficacy evaluation (refer to ICH E9 Guidance).
  - The choice of non-inferiority margin “15%” in the study may seem to be large, assuming the expected patient excellent response rate for cryotherapy group of 90-95% in the protocol.
  - The non-inferiority assessment should be based on one-sided 97.5% confidence interval approach rather than two-sided 90% confidence interval.
2. As only the comparison between Metvix and placebo is of interest in this NDA, only descriptive results are summarized for study 301.

**Results for Study 301**

**1. Patient Disposition and Baseline Characteristics**

One hundred and two subjects were randomized to Metvix PDT. Of these, 97 (95%) of them completed the study and 5 (5%) of them withdrew due to adverse events (2%), lost of follow-up (1%) and other reasons (2%). Ninety-eight subjects (96%) were analyzed for efficacy.

Among the enrolled subjects in Metvix group, sixty-six (65%) subjects are males. The age of the enrolled subjects ranged from 42 to 88 years with a mean age of 71. About 59% of subjects in Metvix group had 1-3 AK lesions at baseline. For baseline lesion characteristics, 384 lesions were included in Metvix PDT group. Of these, 149 (39%), 211 (55%) and 24 (6%) were mild, moderate, and thick in severity, respectively. Two hundred and fifty (65%), 100 (26%) and 34 (9%) lesions were located on the face, scalp and other locations, respectively.

**2. Results**

The efficacy endpoints of interest (from the protocol) were:

- Primary: Patient excellent lesion response rate
- Secondary: Lesion complete response rate

The endpoint of patient complete response rate is also added, as it was recommended by the Agency as the primary in the pivotal trials. Results are presented in Table 10.

**Table 10: Efficacy Results from Study 301**

Efficacy endpoint	Metvix (n=98)	Cryotherapy (n=95)
Patient complete lesion response rate <sup>1</sup>	46/98 (47%)	56/95 (59%)
Patient excellent lesion response rate	54 (55%)	68 (72%)
Lesion complete response rate <sup>2</sup>	252/367 (69%)	250/332 (75%)

Source: Sponsor’s NDA submission (pages 36 and 42, Volume 50).  
<sup>1</sup>Result is reviewer’s summary based on the Sponsor’s electronic SAS data sets (files: les\_.xpt, pdt\_.xpt, demo.xpt).  
<sup>2</sup>Calculation is based on the number of lesions treated.

The summary of Table 10 is:

- The patient complete response rate, patient excellent response rate, and lesion complete response rate for Metvix PDT group are comparable to those in study 302. The response rates are 47%, 55%, and 69% in study 301, as compared to 58%, 58%, and 65% in study 302.
- To investigate the response rates for only mild to moderate AK lesions on the face or scalp; efficacy results are presented in Table CIII.11 of the Appendix. Results from study 301 are similar to those in Table 10. The response rates in study 302 are slightly higher than those in Table 8 (i.e. 62.5%, 62.5%, 71.4% in Table CIII.11 vs. 58%, 58%, 65% in Table 8 for patient complete response, patient excellent response and lesion complete response). However, the difference is small.

As 58 subjects (i.e. 59%) in Metvix group had 1-3 AK lesions at baseline, the results of patient complete response rate by baseline AK lesion count are presented in Table 11. The summary is:

- The patient complete response rates for Metvix treatment in study 301 are comparable to those in study 302 for subjects who had 1, 2, and 3 baseline AK lesions (i.e. 80%, 45%, and 33% in study 301 vs. 78%, 50% and 33% in study 302).
- 40 subjects (i.e. 41%) had 4-10 AK lesions at baseline. The patient complete response rate for Metvix treatment is 38% (i.e. 15/40) for subjects who had 4-10 baseline AK lesion counts. This result is similar to that in study 302, i.e.  $1/3 = 33\%$ .

**Table 11: Patient Complete Lesion Response Rates by Baseline AK Counts: Study 301**

Study 301	Number of Lesions per Patient					Total
	1	2	3	4	5	
Metvix (n=98)	16/20 (80%)	9/20 (45%)	6/18 (33%)	5/10 (50%)	4/6 (67%)	46/98 (47%)
n (%)	6	7	8	9	10	
	2/8 (25%)	2/6 (33%)	1/2 (50%)	0/3	1/5 (20%)	

Source: Summary is based on the Sponsor's electronic SAS data sets (files: les .xpt, pdt .xpt, and demo.xpt).

### 2.6.3 Safety Review of Studies 301 and 302

Safety assessment of Metvix and placebo PDT based on the incidence of adverse events for studies 301 and 302 is summarized in Table 12. The summary is:

- The adverse event incidence rates are 48% vs. 21% for Metvix vs. placebo, which are smaller than those in studies 305 and 306 (i.e. 88% vs. 54%). This could be due to the fact that a smaller number of lesions were treated and most of them (i.e. approximately 91% and 96% of lesions in studies 301 and 302, respectively) were treated with only 1 PDT session in studies 301 and 302, as compared to two PDT sessions in studies 305 and 306.
- The subject discontinuation rates due to adverse events as well as serious adverse event rates are 1.6% vs. 0 for Metvix vs. placebo, which is similar to those in studies 305 and 306 (i.e. 1.5% vs. 0 for Metvix vs. placebo).
- Two deaths are reported in cryotherapy group.

**Table 12: Overall Incidence of Adverse Events: Studies 301 and 302 Combined**

Events	Metvix PDT (n=122)	Placebo PDT (n=19)	Cryotherapy (n=100)
Subjects with at least one adverse event	59 (48%)	4 (21%)	32 (32%)
Total adverse events	121	6	64
Total local adverse events	83	6	42
Adverse events severity and relationship			
Mild:			
Not related to study drug	7	0	11
Uncertain	8	3	1
Related to study drug	35	1	23
Moderate:			
Not related to study drug	6	0	7
Uncertain	6	0	0
Related to study drug	33	2	13
Severe:			
Not related to study drug	2	0	
Uncertain	0	0	3
Related to study drug	3	0	0
			3
Subjects with adverse events resulting in discontinuation	2 (1.6%)	0	2 (2%)
Subjects with serious adverse events	2 (1.6%)	0	3 (3%)
Deaths	0	0	2 (2%)
Source: Sponsor's NDA submission (pages 43, 59-61, Volume 49; pages 52, 85-91, Volume 50).			

## 2.7 Conclusions and Recommendations

The Sponsor in this submission presented results for two pivotal studies (studies 305 and 306) and two Phase 3 studies (studies 301 and 302) in support of the efficacy and safety claim of

Metvix PDT for the treatment of non-hyperkeratotic actinic keratoses (AK).

The topical application of Metvix Cream was in conjunction with the photodynamic therapy (PDT). All enrolled subjects in the four studies are Caucasians. Patients with mild to moderate AK lesions on the face or scalp were recruited in studies 305 and 306. Studies 301 and 302 enrolled subjects with any grades of AK lesions located on any locations. Two treatment sessions of Metvix PDT with 7-day apart were included in the pivotal studies 305 and 306; while only one session was performed for the lesions on the face or scalp in studies 301 and 302. The cream was administered on the lesions for approximately 3 hours, followed by illumination. Efficacy results based on the ITT population with treating missing data as failures are summarized in Table E.1.

### Efficacy:

➤ Comparison to Placebo:

#### Pivotal Trials 305 and 306:

Two-session of Metvix PDT therapy is superior to placebo PDT in the treatment of mild to moderate AK lesions on the face or scalp with respect to:

- Primary: Percentage of subjects with complete lesion response (p-value < 0.001).
- Secondary:
  - Percentage of subjects with excellent lesion response (p-value < 0.001).

- Lesion complete response rate across patients (p-value < 0.001).

Other comments for studies 305 and 306 are:

- Study 306:
  - Investigators might be able to differentiate the treatment assignment at the visit of the 2<sup>nd</sup> treatment session even though nurses administered illumination and recording of local adverse events. This is because two sessions were only 7 days apart. The adverse events (i.e. crusting, blisters, erythema, and burning sensation skin) resulted from the 1<sup>st</sup> session might not be well resolved by the time of the 2<sup>nd</sup> treatment session following a discussion with the clinical reviewer. However, sensitivity analyses show that Metvix PDT is overall better than placebo PDT even when susceptible subjects are imputed as failures.
- Study 305:
  - Blinding might be an issue even though the lesion response was evaluated 3 months after treatments, as the investigators rather than other party handled the illumination procedure and recording of local adverse events. However, Table E.1 shows the consistency of response rates (i.e. patient complete response, patient excellent response, and lesion complete response) for Metvix PDT between studies 305 and 306.
  - In contrast to study 306, where all subjects had 4-10 AK lesions, only 27 (31%) and 7 (30%) subjects in Metvix and placebo, respectively, had 4-10 AK lesions at baseline in study 305. This might need to be reflected in the labeling even though Metvix is statistically better than placebo when only subjects with 4-10 AK lesions were analyzed (i.e. patient complete response rates of 67% vs. 0 for Metvix vs. placebo with p-value = 0.0075).
  - The study was conducted in Australia. It is a matter of the clinical judgement of the medical division to decide whether study 305 is adequate for efficacy extrapolation to the US population.

**Table E.1: Summary of Efficacy Results**

Pivotal	Efficacy endpoints	Metvix PDT	Placebo PDT	Comparison
Study 305	Primary: Patient complete response rate	71/88 (81%)	3/23 (13%)	< 0.001
	Secondary: Patient excellent response rate	76/88 (86%)	4/23 (17%)	< 0.001
	Lesion complete response rate	317/360 (88%)	21/74 (28%)	< 0.001
Study 306	Primary: Patient complete response rate	33/42 (79%)	8/38 (21%)	< 0.001
	Secondary: Patient excellent response rate	35/42 (83%)	12/38 (32%)	< 0.001
	Lesion complete response rate	221/260 (85%)	92/242 (38%)	< 0.001
<b>Supportive Phase 3 Trials</b>				
Study 301	Patient complete response rate	46/98 (47%)	N/A	N/A
	Patient excellent response rate	54/98 (55%)		
	Lesion complete response rate	252/367 (69%)		
Study 302	Patient complete response rate	11/19 (58%)	2/18 (11%)	< 0.001
	Patient excellent response rate	11/19 (58%)	2/18 (11%)	< 0.001
	Lesion complete response rate	32/49 (65%)	6/36 (17%)	< 0.001

Phase 3 Studies 301 and 302:

The efficacy claim of Metvix PDT for mild to moderate AK lesions may be supported in study 302, depending upon the baseline AK lesion counts considered in the labeling, as:

- 16 (84%) and 17 (94%) subjects had less than 4 AK lesions at baseline in Metvix and placebo groups, respectively. The patient complete response rates for Metvix vs. placebo are 63% vs. 12%, which are comparable to the overall patient complete response rates for the entire study (i.e. 58% vs. 11%).
- Only 3 (16%) and 1 (6%) subjects had 4-10 AK lesions at baseline in Metvix and placebo groups. The patient complete response rates are 33% vs. 0 for Metvix vs. placebo.

For study 301, it is difficult to assess a reliable estimate of the treatment effect for Metvix PDT treatment, as no placebo arm was included. However, it should be noted that the response rates for Metvix treatment in study 301 are comparable to those in study 302:

- The overall patient complete response rate, patient excellent response rate and lesion complete response rate are 47%, 55% and 69% in study 301, as compared to 58%, 58% and 65% in study 302.
- For subjects who had 1, 2, and 3 baseline AK lesions, the patient complete response rates are 80%, 45% and 33%, respectively, in study 301, which are comparable to those in study 302 (i.e. 78%, 50% and 33%).
- For subjects who had 4-10 baseline AK lesions, the patient complete response rate for Metvix treatment is 38% (= 15/40) in study 301, which is similar to that in study 302, i.e. 33% = 1/3.

It is a clinical judgement \_\_\_\_\_ should be granted.

- As the Sponsor's labeling claims \_\_\_\_\_  
\_\_\_\_\_ the following are comments concerning such evaluation:

- All enrolled subjects in the four trials are Caucasians. Whether or not Caucasian is the primary treated population for AK indication, it is a clinical issue.

Safety:

Safety assessment for pivotal studies 305 and 306 (i.e. 2 treatment PDT sessions) based on the incidence of adverse events is:

- A higher percentage of patients had at least one adverse event in Metvix PDT group as compared to placebo arm (88% vs. 54%).

- Most adverse events in Metvix group were local adverse events. Among them, 99% of the events (i.e. 298/301) were treatment-related and most were mild to moderate in severity.
- Burning sensation skin and erythema were the most common local adverse events for Metvix and placebo PDT (23%, 21% in Metvix and 18%, 27% in placebo).

Safety assessment for studies 301 and 302 based on the incidence of adverse events is:

- The adverse event incidence rates are 48% vs. 21% for Metvix vs. placebo, which are smaller than those in studies 305 and 306. This could be due to the fact that a smaller number of lesions were treated and most of them (i.e. approximately 91% and 96% of lesions in studies 301 and 302, respectively) were treated with only 1 PDT session, as compared to two PDT sessions in studies 305 and 306.
- The subject discontinuation rates due to adverse events as well as serious adverse event rates are 1.6% vs. 0 for Metvix vs. placebo, which are similar to those in studies 305 and 306, 1.5% vs. 0 for Metvix vs. placebo.

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Concur: Mohamed Alosh, Ph.D.  
Team Leader, Biometrics III

cc:

Archival: NDA 21-415/N-000  
HFD-540/Div. File  
HFD-540/Dr. Wilkin  
HFD-540/Dr. Walker  
HFD-540/Dr. Vaughan  
HFD-540/Ms. Lutwak  
HFD-710/Dr. Anello  
HFD-725/Dr. Huque  
HFD-725/Dr. Alosh  
HFD-725/Dr. Lee

This review contains 42 pages (1 cover page, 1 page of table of contents, 4 pages of executive summary, 22 pages of text and 14 pages of Appendix).

## APPENDIX A

### Randomization/Blinding Procedures

#### **Study 305 (conducted in Australia during March 2000 – December 2000):**

The Sponsor's randomization codes were prepared based on computer-generated numbers prior to start of the trial (i.e. 1/19/2000), and the first patient was enrolled on 3/1/2000 (per documentation in the Sponsor's NDA submission, pages 4-27 and 72, Volume 47). The treatment assignment was done in a sequential order of patient enrollment within each center. Upon enrollment, each patient was given the envelope corresponding to the assigned patient number. It should be noted that, according to the Sponsor, the investigators were not blinded from the allocation of PDT and cryotherapy due to the different nature of PDT and cryotherapy treatments. However, they were blinded from the allocation of Metvix PDT and placebo PDT.

Even though the Sponsor indicated that the allocation within PDT groups (i.e. to Metvix PDT or placebo PDT) was double-blinded, it should be noted that, according to the Sponsor, patients receiving Metvix PDT are expected to have a higher rate of local phototoxic reactions during illumination than patients given placebo. The procedures related to administration of light, and recording of local adverse events during illumination were handled by the investigators. This might introduce bias into efficacy evaluation.

#### **Study 306 (conducted in US during June 2000 – February 2001):**

Five centers were included in study 306. The Sponsor's randomization codes for the four study centers (i.e. Norfolk, Santa Monica, Cincinnati, and Clinton Township) were prepared based on computer-generated numbers prior to start of the trial (i.e. 4/11/2000). The first patient was enrolled on 6/10/2000 (per documentation in the Sponsor's NDA submission, pages 235-245, Volume 43, and page 8, Volume 44). The enrolled patients were randomized in an equal allocation to Metvix PDT and placebo PDT. The treatment assignment was done in a sequential order of patient enrollment within each center.

A protocol amendment #4 for the addition of the center in Austin, Texas, was dated 8/22/2000. According to the Sponsor, the rationale was that patient enrollments in the other 4 centers were slower than expected. Consequently, an additional center was opened. The 1<sup>st</sup> patient enrollment date in the center was 9/28/00. The impact of the center on the efficacy results is discussed in the efficacy review section.

It should be noted that the conduct of study 306 seems to be in a double-blind fashion, as:

- The Metvix and placebo creams were of identical appearance.
- Center nurses administered the illumination and recording of local adverse events for PDT therapies (i.e. Metvix PDT or placebo PDT). The investigator prepared lesions at each session, and evaluated the lesion response and cosmetic outcome at the 3-month post-treatment.

However, the clinical reviewer had concerns that investigators might be able to differentiate the treatment assignments at the visit of the 2<sup>nd</sup> treatment session based on the residual safety

measures, i.e. crusting, blisters, erythema and burning sensation skin, as a result from the 1<sup>st</sup> treatment session. This is because the two sessions were only 7 days apart and some safety measures might not be well resolved by the time of the 2<sup>nd</sup> treatment session. The summary of subjects with local adverse events of crusting, blisters, erythema and burning sensation skin is presented in Table A.1. Even though the lesion evaluation was conducted 3 months after treatment and these events were resolved by then, sensitivity analyses are performed to evaluate the impact of such possible bias on the efficacy results. Details are discussed in the section of statistical and technical issues.

**Table A.1: Summary of Subjects with Local Adverse Events**

Adverse Event	STUDY 305		STUDY 306	
	Metvix (n=88)	Placebo (n=23)	Metvix (n=42)	Placebo (n=38)
Burning Sensation Skin	43 (49%)	4 (17%)	27 (64%)	5* (13%)
Erythema	42 (48%)	4 (17%)	22 (52%)	8 (21%)
Crusting	4 (5%)	0	16 (38%)	6 (16%)
Blisters	6 (7%)	0	8 (19%)	2 (5%)

**Source:** Summary is based on the Sponsor's electronic SAS data sets (files: ae\_\*.xpt, and pdt\_\*.xpt).  
 \* number is different from the Sponsor's NDA submission (i.e. 5 vs. 4 on page 52, Volume 42). The five subjects in Sponsor's electronic SAS data set are 2013, 4008, 4012, 4017 and 5004.

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## APPENDIX B

### Patient's Weighted Mean Lesion Response

According to the Sponsor, the computation takes into account the baseline AK lesion counts per patient and is formulated below:

let

$n_i$  = number of lesions within one patient  
 $c_i$  = number of lesions in complete response within one patient at 3-month post-treatment  
 $x_i = 100\% c_i / n_i$  = lesion response rate within one patient at 3-month post-treatment  
 $N_t$  = total number of patients within one treatment arm  
 $n_t$  = total number of lesions within one treatment arm  
 $w_i = n_i / n_t$  = weight (in terms of baseline lesion counts) for one patient

with  $\sum_{i=1}^{N_t} w_i = 1$  for each treatment, where weight is proportional to the number of lesions for each patient within the corresponding treatment arm. Therefore, the patient's weighted mean lesion response is calculated by  $\sum_{i=1}^{N_t} w_i x_i$ .

#### Reviewer's Comment:

It should be noted that the formulation of patient's weighted mean lesion response is algebraically the same as lesion complete response rate across patients. The lesion complete response rate across patients is one of the secondary efficacy endpoints specified. To see this, note that

$$\sum_{i=1}^{N_t} w_i x_i = \sum_{i=1}^{N_t} \frac{n_i}{n_t} 100\% \frac{c_i}{n_i} = 100\% \sum_{i=1}^{N_t} \frac{c_i}{n_t} = 100\% \frac{c_1 + c_2 + \dots + c_{N_t}}{n_1 + n_2 + \dots + n_{N_t}},$$

which is the lesion complete response rate across patients within one treatment arm.

As commented by the Agency at the End-of-Phase 2 meeting (dated 6/22/2000), lesion complete response rate has the advantage of being readily comprehensible to patients and practitioners, but not patient's weighted mean lesion response.

APPENDIX C

Table CIII.1: Patient Enrollment and Treatment by Center

Study 305 (Australia)	Center	Patients randomized			Number of patient treated		
		Metvix	Placebo	Cryotherapy	Metvix	Placebo	Cryotherapy
		9	2	11	7 (78%)	2 (100%)	11 (100%)
		18	4	18	18 (100%)	4 (100%)	18 (100%)
		13	3	12	12 (92%)	3 (100%)	12 (100%)
	Adelaide -	9	2	9	9 (100%)	2 (100%)	9 (100%)
	Adelaide - Reid	6	3	3	6 (100%)	3 (100%)	3 (100%)
		9	2	9	9 (100%)	2 (100%)	8 (89%)
	Liverpool	7	2	9	7 (100%)	2 (100%)	9 (100%)
	Newcastle	5	1	5	5 (100%)	1 (100%)	5 (100%)
	Perth	15	4	14	15 (100%)	4 (100%)	14 (100%)
	Total	91	23	90	88 (97%)	23 (100%)	89 (99%)

  

Study 306 (US)	Center	Patients randomized		Number of patient treated	
		Metvix	Placebo	Metvix	Placebo
	Norfolk	10	8	10	8
	Santa Monica	12	12	12	12
	Cincinnati	4	3	4	3
	Clinton Township	10	9	10	9
	Austin	6	6	6	6
	Total	42	38	42 (100%)	38 (100%)

Source: Sponsor's NDA submission (page 63, Volume 42; pages 67-68, Volume 45).

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**Table CIII.2: Patient Demographics and Baseline Characteristics:  
 Studies 305 and 306 – ITT Population**

STUDY 305	Metvix (n=88)	Placebo (n=23)	Cryotherapy (n=89)	p-value*
<b>Age (years)</b>				
Mean (s.d.)	64 (13)	66 (11)	65 (12)	0.5069
Range	33 – 86	49 – 89	38 – 86	
<b>Gender, n (%)</b>				0.2309
Male	49 (56%)	16 (70%)	54 (61%)	
Female	39 (44%)	7 (30%)	35 (39%)	
<b>Race, n (%)</b>				1.000
White	88 (100%)	23 (100%)	89 (100%)	
<b>Skin Prototype, n (%)</b>				0.4722
Type I	32 (36%)	12 (52%)	30 (34%)	
Type II	38 (43%)	6 (26%)	41 (46%)	
Type III	15 (17%)	4 (17%)	17 (19%)	
Type IV	3 (3%)	1 (4%)	1 (1%)	
<b>Lesion numbers, n (%)</b>				0.9613
Below 4	55 (62.5%)	15 (65%)	55 (62%)	
4 – 5	13 (15%)	4 (17%)	8 (9%)	
6 – 7	7 (8%)	2 (9%)	7 (8%)	
8 – 10	7 (8%)	1 (4%)	8 (9%)	
Above 10	6 (7%)	1(4%)	11 (12%)	
<b>Lesion severity <sup>1</sup>, n/N (%)</b>				0.0897
Mild (thin)	209/360 (58%)	35/74 (47%)	232/421 (55%)	
Moderate	151/360 (42%)	39/74 (53%)	189/421 (45%)	
<b>Lesion location <sup>1</sup>, n (%)</b>				0.1381
Face	273/360 (76%)	62/74 (84%)	284/421 (67%)	
Scalp	87/360 (24%)	12/74 (16%)	137/421 (33%)	
<b>STUDY 306</b>	<b>Metvix (n=42)</b>	<b>Placebo (n=38)</b>		<b>p-value*</b>
<b>Age (years)</b>				
Mean (s.d.)	64 (13)	67 (12)		0.2865
Median (range)	67 (31 – 84)	72 (39 – 84)		
<b>Gender, n (%)</b>				0.6139
Male	36 (86%)	34 (89%)		
Female	6 (14%)	4 (11%)		
<b>Race, n (%)</b>				1.000
White	42 (100%)	38 (100%)		
<b>Skin Prototype, n (%)</b>				0.7520
Type I	11 (26%)	9 (24%)		
Type II	19 (45%)	16 (42%)		
Type III	8 (19%)	11 (29%)		
Type IV	3 (7%)	2 (5%)		
Type V	1 (2%)	0		
<b>Lesion numbers, n (%)</b>				0.6296
4 – 5	18 (43%)	18 (47%)		
6 – 7	14 (33%)	9 (24%)		
8 – 10	10 (24%)	11 (29%)		
<b>Lesion severity <sup>1</sup>, n/N (%)</b>				0.0368
Mild (thin)	196/260 (75%)	162/242 (67%)		
Moderate	64/260 (25%)	80/242 (33%)		
<b>Lesion location <sup>1</sup>, n (%)</b>				0.4021
Face	226/260 (87%)	204/242 (84%)		
Scalp	34/260 (13%)	38/242 (16%)		
Source: Summary is based on the Sponsor's NDA submission (pages 36, 65 and 72, Volume 42; pages 70-71, 77-78, Volume 45)				
<sup>1</sup> Based on the total number of lesions across patients identified at baseline.				
*p-value is for the comparability purpose between Metvix PDT and placebo PDT groups and is obtained by the reviewer based on ANOVA for continuous data and Cochran-Mantel-Haenszel test adjusting for site for categorical data.				

**Table CIII.3 (a): Patient Complete Response Rate by Baseline AK Counts: ITT Population**

Study 305	Number of Lesions per Patient					Total
	Below 4	4-5	6-7	8-10	Above 10	
Metvix (n=88)	49/55 (89%)	9/13 (69%)	4/7 (57%)	5/7 (71%)	4/6 (67%)	71/88 (81%)
Placebo (n=23)	3/15 (20%)	0/4	0/2	0/1	0/1	3/23 (13%)
Cryotherapy (n=89)	41/55 (75%)	6/8 (75%)	2/7 (29%)	0/8	2/11 (18%)	51/89 (57%)

  

Study 306	Number of Lesions per Patient			Total
	4-5	6-7	8-10	
Metvix (n=42)	17/18 (94%)	11/14 (79%)	5/10 (50%)	33/42 (79%)
Placebo (n=38)	5/18 (28%)	2/9 (22%)	1/11 (9%)	8/38 (21%)

**Source:** Results in study 305 are obtained by the reviewer based on the Sponsor's electronic SAS data sets (files: les\_xpt, pdt\_xpt, and demo.xpt). Results in study 306 are based on the Sponsor's NDA submission (page 85, Volume 42).

**Table CIII.3 (b): Patient Complete Response Rate by Baseline AK Counts  
 ITT Population**

Study 305	Metvix (n=88)	Placebo (n=23)	Cryotherapy (n=89)
<b>Lesion number</b>			
1	22/22 (100%)	2/7 (29%)	17/19 (89%)
2	24/26 (92%)	1/6 (17%)	16/20 (80%)
3	3/7 (43%)	0/2	8/16 (50%)
4	8/10 (80%)	0/3	3/4 (75%)
5	1/3 (33%)	0/1	3/4 (75%)
6	4/6 (67%)	0/2	2/6 (33%)
7	0/1	--	0/1
8	3/4 (75%)	--	0/2
9	1/2 (50%)	0/1	0/3
10	1/1 (100%)	--	0/3
11	--	0/1	0/3
12	1/1 (100%)	--	0/3
13	1/1 (100%)	--	--
14	--	--	2/2 (100%)
15	1/1 (100%)	--	--
16	0/1	--	0/1
23	0/1	--	--
24	--	--	0/1
25	--	--	0/1
28	1/1 (100%)	--	--
<b>Total</b>	<b>71/88 (81%)</b>	<b>3/23 (13%)</b>	<b>51/89 (57%)</b>

  

Study 306	Metvix (n=42)	Placebo (n=38)	
<b>Lesion number</b>			
4	11/11 (100%)	2/7 (29%)	
5	6/7 (86%)	3/11 (27%)	
6	5/6 (83%)	1/3 (33%)	
7	6/8 (75%)	1/6 (17%)	
8	2/3 (67%)	1/4 (25%)	
9	2/5 (40%)	0/3	
10	1/2 (50%)	0/4	
<b>Total</b>	<b>33/42 (79%)</b>	<b>8/38 (21%)</b>	

**Source:** summary is based on the Sponsor's electronic SAS data sets (files: les\_xpt, pdt\_xpt and demo.xpt)

**Table CIII.4: Patient Complete Response Rate by Center: ITT Population**

<b>Study 305</b>			
<b>Center</b>	<b>Metvix (n=88)</b>	<b>Placebo (n=23)</b>	<b>Cryotherapy (n=89)</b>
	2/7 (29%)	0/2	4/11 (36%)
	14/18 (78%)	0/4	14/18 (78%)
	10/12 (83%)	0/3	7/12 (58%)
<b>Adelaide</b>	7/9 (78%)	0/2	4/9 (44%)
<b>Adelaide - Reid</b>	4/6 (67%)	2/3 (67%)	3/3 (100%)
	9/9 (100%)	0/2	0/8
<b>Liverpool</b>	6/7 (86%)	0/2	3/9 (33%)
<b>Newcastle</b>	5/5 (100%)	0/1	2/5 (40%)
<b>Perth</b>	14/15 (93%)	1/4 (25%)	14/14 (100%)
<b>Total</b>	71/88 (81%)	3/23 (13%)	51/89 (57%)
<b>Study 306</b>			
<b>Center</b>	<b>Metvix (n=42)</b>	<b>Placebo (n=38)</b>	
<b>Norfolk</b>	8/10 (80%)	2/8 (25%)	
<b>Santa Monica</b>	10/12 (83%)	3/12 (25%)	
<b>Cincinnati</b>	3/4 (75%)	1/3 (33%)	
<b>Clinton Township</b>	7/10 (70%)	1/9 (11%)	
<b>Austin</b>	5/6 (83%)	1/6 (17%)	
<b>Total</b>	33/42 (79%)	8/38 (21%)	

Source: Results in study 305 are obtained by the reviewer. Results of study 306 are based on the Sponsor's NDA submission (page 84, Volume 42).

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**Table CIII.5: Patient Excellent Lesion Response Rate by Baseline AK Counts  
 ITT Population (Reviewer's Analysis)**

Study 305	Number of Lesions per Patient					Total
	Below 4	4 - 5	6 - 7	8 - 10	Above 10	
Metvix (n=88)	49/55 (89%)	11/13 (85%)	5/7 (71%)	6/7 (86%)	5/6 (83%)	76/88 (86%)
Placebo (n=23)	3/15 (20%)	1/4 (25%)	0/2	0/1	0/1	4/23 (17%)
Cryotherapy (n=89)	41/55 (75%)	7/8 (88%)	4/7 (57%)	5/8 (63%)	4/11 (36%)	61/89 (69%)
Study 306	Number of Lesions per Patient				Total	
		4 - 5	6 - 7	8 - 10		
Metvix (n=42)		17/18 (94%)	13/14 (93%)	5/10 (50%)	35/42 (83%)	
Placebo (n=38)		7/18 (39%)	3/9 (33%)	2/11 (18%)	12/38 (32%)	

Source: Results are based on the Sponsor's electronic SAS data sets (files: les .xpt, pdt .xpt, and demo.xpt)

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**Table CIII.6: Lesion Complete Response Rate by Baseline Lesion Severity  
 ITT population**

<b>Study 305</b>	<b>Grade 1 (AK thin)</b>	<b>Grade 2 (AK moderate)</b>	<b>Total</b>
Metvix (c=360)	198/209 (95%)	119/151 (79%)	317/360 (88%)
Placebo (c=74)	12/35 (34%)	9/39 (23%)	21/74 (28%)
Cryotherapy (c=421)	144/232 (62%)	139/189 (74%)	283/421 (67%)
<b>Study 306</b>	<b>Grade 1 (AK thin)</b>	<b>Grade 2 (AK moderate)</b>	<b>Total</b>
Metvix (c=260)	172/196 (88%)	49/64 (77%)	221/260 (85%)
Placebo (c=242)	72/162 (44%)	20/80 (25%)	92/242 (38%)

Source: Sponsor's NDA submission (page 89, Volume 42; page 82, Volume 45)

**Table CIII.7: Lesion Complete Response Rate by Lesion Location – ITT Population**

<b>Study 305</b>	<b>Face</b>	<b>Scalp</b>	<b>Total</b>
Metvix (c=360)	251/273 (92%)	66/87 (76%)	317/360 (88%)
Placebo (c=74)	15/62 (24%)	6/12 (50%)	21/74 (28%)
Cryotherapy (c=421)	196/284 (69%)	87/137 (64%)	283/421 (67%)
<b>Study 306</b>	<b>Face</b>	<b>Scalp</b>	<b>Total</b>
Metvix (c=260)	195/226 (86%)	26/34 (76%)	221/260 (85%)
Placebo (c=242)	73/204 (36%)	19/38 (50%)	92/242 (38%)

Source: Sponsor's NDA submission (page 89, Volume 42; page 82, Volume 45)

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**Table CIII.8: The Impact of Missing Data on the Overall Efficacy Results  
 ITT Population (Reviewer's Analysis based on the Worst Case Scenario †)**

<b>Study 305</b>	<b>Metvix (n=88)</b>	<b>Placebo (n=23)</b>	<b>Cryotherapy (n=89)</b>	<b>Comparison*</b>
<b>Primary:</b> Patient complete response rate	71/88 (81%)	3/23 (13%)	51/89 (57%)	< 0.001
<b>Secondary:</b> Patient excellent response rate Lesion complete response rate	76/88 (86%) 317/360 (88%)	4/23 (17%) 21/74 (28%)	61/89 (69%) 283/421 (67%)	< 0.001 < 0.001
<b>Study 306</b>	<b>Metvix (n=42)</b>	<b>Placebo (n=38)</b>		<b>Comparison*</b>
<b>Primary:</b> Patient complete response rate	33/42 (79%)	8/38 (21%)		< 0.001
<b>Secondary:</b> Patient excellent response rate Lesion complete response rate	35/42 (83%) 221/260 (85%)	12/38 (32%) 93/242 (38%)		< 0.001 < 0.001
*p-value is the comparison between Metvix PDT and placebo PDT based on Cochran-Mantel-Haenszel test adjusting for study site.				
†Worst case scenario: impute missing data as failures in Metvix group and successes in placebo group.				

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**Table CIII.9: Cream Application and Illumination Procedure – Studies 305 and 306**

STUDY 305	Metvix PDT			Placebo PDT		
	n	Mean (s.d.)	Range	n	Mean (s.d.)	Range
Illumination time (mm:ss)	311	9:54 (4:02)	0:39 – 27:50	76	11:00 (4:17)	4:30 – 23:40
Light dose (J/cm <sup>2</sup> )	309	75.8 (8.5)	4.1 – 110.5	76	77.0 (5.2)	51.5 – 107.3
Light intensity (mW/cm <sup>2</sup> )	309	145.5 (52.4)	46 – 386	76	134.2 (49.4)	54 – 285
Light field diameter (mm)	312	42.7 (7.6)	25 – 55	76	43.9 (8.4)	30 – 55
Cream application time (hh:mm)	314	3:12 (0:16)	2:10 – 4:25	76	3:07 (0:13)	3:00 – 4:20
STUDY 306	Metvix PDT			Placebo PDT		
	n	Mean (s.d.)	Range	n	Mean (s.d.)	Range
Illumination time (mm:ss)	81	8:43 (1:18)	5:00 – 12:01	76	8:41 (1:01)	6:42 – 10:56
Light dose (J/cm <sup>2</sup> )	81	77.7 (3.9)	50.4 – 87.8	76	78.2 (2.8)	74.9 – 90.5
Light intensity (mW/cm <sup>2</sup> )	81	153.2 (18.6)	114.1 – 190.6	76	154.4 (17.2)	119 – 189.8
Light field diameter (mm)	81	41.0 (2.8)	35 – 50	76	40.4 (2.6)	35 – 47.1
Cream application time (hh:mm)	81	3:12 (0:15)	2:31 – 4:23	76	3:11 (0:13)	3:00 – 4:19

Source: Summary is based on the Sponsor's electronic SAS data sets (file: pdt .xpt)

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**Table CIII.10: Lesion Complete Response Rate by Baseline Lesion Severity and Lesion Location – Study 302**

Study 302	Lesion Description	Face/Scalp	Other Location	Total
Metvix (c=49)	Mild (thin) (c=11)	6/10 (60%)	1/1 (100%)	7/11 (64%)
	Moderate (c=34)	24/32 (75%)	1/2 (50%)	25/34 (74%)
	Thick (c=4)	0/4	--	0/4
	Total	30/46 (65%)	2/3 (67%)	32/49 (65%)
Placebo (c=36)	Mild (thin) (c=17)	4/17 (24%)	--	4/17 (24%)
	Moderate (c=17)	2/17 (12%)	--	2/17 (12%)
	Thick (c=2)	0/2	--	0/2
	Total	6/36 (17%)	--	6/36 (17%)

**Source:** Sponsor's NDA submission (page 38, Volume 49).

**Table CIII.11: Response Rates for Mild to Moderate Lesions on Face or Scalp Studies 301 and 302 (Reviewer's Summary)**

Study	Efficacy endpoints	Metvix	Placebo
301	Patient complete response rate	41/85 (48%)	N/A
	Patient excellent response rate	48/85 (56%)	
	Lesion complete response rate	218/314 (69%)	
302	Patient complete response rate	10/16 (62.5%)	2/17 (12%)
	Patient excellent response rate	10/16 (62.5%)	2/17 (12%)
	Lesion complete response rate	30/42 (71.4%)	6/34 (18%)

**Source:** Summary is based on the Sponsor's electronic SAS data sets (files: pdt\_.xpt, les\_.xpt and demo.xpt).

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## APPENDIX D

### Randomization Procedure in Study 302

According to the Sponsor's protocol (dated 4/9/99), the treatment allocation was based on the stratification according to center and the number of baseline AK lesions (i.e. categories were 1-3, 4-7 and 8-10). An electronic randomization list, which was used to allocate patient numbers consecutively either to Metvix or placebo, was kept on a user-protected area on the server at — (page 19, Volume 49). However, no such list was included in the Sponsor's NDA submission (dated 9/26/01).

The Sponsor made amendment #2 on 7/7/1999; a central randomization procedure was implemented during the course of the trial. The investigator contacted the Sponsor by telephone or fax each time a patient was to be included in the study to receive the treatment allocation.

To identify any randomization issue for the trial, the patient number and treatment allocation was examined (per pages 268-269, Volume 49 and Sponsor's SAS electronic data sets). As the information provided on 9/26/01 was not sufficient, the Agency had made requests on the following points (dated 3/26/02 and 5/2/02). Sponsor's responses were submitted via fax on 4/19/02 and 5/6/02, respectively.

- Agency's request on 3/26/02:
  1. Please explain whether the randomization was done prior to patient enrollment in the trial based on computer generated list. If so, please provide such treatment allocation list.
  2. How many centers were planned to participate in the trial and number of patients planned to be enrolled in each center?
  3. Please explain whether randomization was done centrally (i.e. study level) or on the investigator level (i.e. randomization was done per investigator basis). Please explain any deviations from the pre-planned randomization procedure.
  4. If patient allocations were not in sequence, please provide an explanation on such cases.
  
- Agency's request on 5/2/02 (for the clarification on the fax dated 4/19/02):
  1. The Sponsor indicated that patients were allocated sequentially within center and stratum. However, one shipment of medication packed according to the randomization list was allocation for Center 4 ( — ), but later was re-labeled for use at Center 1 ( — ) (i.e. patients IDs: 4006, 4007, 4008, 4009, and 4029). Please clarify such change in treatment package allocation.
  2. Subjects 4013, 4014, 4015, and 4016 had 2, 1, 1, and 1-baseline AK lesions (pages 295-300, Volume 49, and Sponsor's SAS electronic data sets). However, they were randomized based on the stratum of baseline lesion number category 4-7 (submission dated 4/19/02). On the other hand, subjects 4025, 4026, 4027 had 1, 3, and 3 baseline AK lesions. However, they were randomized based on the stratum of baseline lesion number category 8-10. Please clarify why these patients were not in the correct strata.

The Sponsor's responses (dated 4/19/02 and 5/6/02) are summarized below:

- (a) Four centers with a total of 40 subjects were pre-planned for the trial. The randomization was done based on center and the stratum of baseline lesion counts (i.e. 1-3, 4-7, and 8-10 lesions) prior to start of the trial. Twelve randomization codes were generated per stratum per center on 4/27/99 and the 1<sup>st</sup> subject was enrolled on 6/7/99.
- (b) The patient recruitment in Center 1 started early and enrolled quickly, whereas the other centers were slow. By the time of amendment #2 (dated 7/7/1999) for the implementation of central randomization procedure, 14 subjects were enrolled and they were all in Center 1.
- (c) As no treatment package for lesion category 1-3 was left, the shipment prepared for Center 4 was re-labeled for the use in Center 1 (Moss).
- (d) Since the treatment packages of stratum 1 (i.e. 1-3 lesions) for Center 4 were shipped for the use in Center 1 and since the majority patients enrolled had 1-3 baseline AK lesions, consequently, rather than producing new treatment packages, the re-allocation of treatment packages from stratum 3 to stratum 1 (i.e. IDs: 4025-4028) as well as from stratum 2 to stratum 1 (i.e. IDs: 4013-4016) occurred on 9/1/1999 and 9/9/1999, respectively.

From this reviewer's point of view, Sponsor's responses seem reasonable. However, to investigate the impact of points (c) and (d) stated above on efficacy results, patients' complete response rates were examined. The findings are:

1. For shipment re-labeled for the use at Center 1, three and 2 subjects were in Metvix and placebo group, respectively. The patient complete response rates were 1/3 (= 33%) vs. 0 for Metvix vs. placebo, which is not expected to affect the overall conclusion.
2. For subjects who had less than 4 AK lesions, but randomized according to higher numbers of lesion category, four and 3 subjects were in Metvix and placebo, respectively. All subjects did not achieve the clearing of all lesions (i.e. patient complete response). Consequently, no impact on the efficacy results is indicated.

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