CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022259Orig1s000

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22259 / 000 RS
Drug Name:	Tolak (fluorouracil) cream 4%
Indication(s):	Actinic Keratoses
Applicant:	Hill Dermaceuticals
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Biometrics Division:	Division of Biometrics III
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1 Executive Summary

The original application for NDA 22259 (submitted on 8/20/2007) contained two Phase 3 trials (Study 48 and Study 49). Studies 48 and 49 were designed to assess the efficacy and safety of Tolak (fluorouracil) cream 4% in the treatment of actinic keratoses (AK). Both Study 48 and Study 49 demonstrated that Tolak was superior to its vehicle in the treatment of AK. The original statistical review (dated 4/4/2008) concluded that the efficacy of Tolak cream 4% had been demonstrated in two studies.

On 6/29/2009, the applicant was issued a Complete Response letter citing deficiencies in the application related to product quality and facility inspections. The Complete Response letter did not list any issues regarding the clinical trials. Note also that nearly nine months into the original review cycle (5/7/2008), the applicant submitted an amendment containing the results of a 12-month open-label follow-up study (Study 50) assessing for recurrence, long-term safety, and retreatment in subjects treated with Tolak in either Study 48 or 49. However, the datasets for this study were not submitted in a usable format. Due to the lateness of the amendment in the original review cycle, the lack of usable datasets, and the pending Complete Response action, Study 50 was not reviewed in the initial review cycle.

The current resubmission (submitted on 12/18/2014) includes information to address the product quality and facility inspection deficiencies listed in the Complete Response letter. The applicant has updated their proposed labeling to include results from the 12-month follow-up study. This review will focus on the results of Study 50 and the corresponding labeling proposal.

The conclusion of the original statistical review that the efficacy of Tolak in the treatment of AK was demonstrated in two vehicle-controlled studies remains the same. The primary efficacy endpoint results (100% clearance of lesions 4 weeks post-treatment for Tolak versus vehicle) for Studies 48 and 49 are presented in Table 1. The two studies combined enrolled 403 subjects on the Tolak arm, of which 204 were classified as having 100% clearance at the end of the study.

Table 1 – 100% Clearance Rates (Studies 48 and 49)

	Tolak 4%	Vehicle	p-value
Study 048	N=353	N=70	
100% Clearance	192 (54%)	3 (4%)	<0.001
Study 049	N=50	N=50	
100% Clearance	12 (24%)	2 (4%)	0.004

Study 50 enrolled 310 of the 403 subjects who had been treated with Tolak in Study 48 or 49. Subjects were to be assessed for recurrence twice in Study 50—at least 6 months after completing Study 48/49 and 12 months after completing Study 48/49. Subjects who had achieved clearance in Study 48/49 were to be evaluated for recurrence, and subjects with lesions present were to be offered re-treatment with Tolak.

The protocol for Study 50 defined recurrence or non-recurrence as follows:

- Subjects with no new AK lesions in the treatment areas upon entry into Study 50 were to be considered to have no recurrence and evaluated again for recurrence 12 months after the completion of Study 48/49.
- Subjects who were completely clear of lesions at the end of Study 48/49, but who had new AK lesions upon entry into Study 50 were considered to have a recurrence.
- Subjects who were not completely clear of lesions at the end of Study 48/49 could be re-treated with Tolak in Study 50. Subjects who were clear of lesions after this additional round of treatment would be assessed for recurrence at the Month 12 visit.

After the initial look at the data, the applicant decided that the above definition did not account for certain unanticipated situations that had occurred in the study. The applicant then created a different definition for assessing recurrence and non-recurrence that modified the population of subjects followed for recurrence by including some subjects who had not been clear at the end of Study 48/49 and also excluding some subjects who had been completely clear of lesions at the end of Study 48/49, but were difficult to assess in Study 50. For example, for the assessment at the first follow-up visit in Study 50 (at least 6 months after completing Study 48/49), recurrence and non-recurrence were defined as follows:

- Recurrence – clear at the end of Study 48/49 and lesions present at the start of Study 50
- Non-recurrence – clear at the end of Study 48/49 and clear at the start of Study 50 OR lesions present at the end of Study 48/49 and clear at the start of Study 50

Note that this analysis excluded all subjects who

- had additional treatments applied before the start of Study 50
- did not enroll in Study 50

The rules for defining recurrence and non-recurrence at Month 12 or overall were even more complex, as they also assessed subjects who received re-treatment with Tolak during Study 50.

The subjects used in the applicant's recurrence analysis include a mixture of subjects who were clear and not clear at the end of Study 48/49. The subset of subjects selected differs for each analysis (0-6 months, 6-12 months, and overall), primarily as a result of dropping subjects from the 6-12 month analysis (but not the overall analysis) who used alternate therapies (not Tolak) during the study after being classified as having a recurrence and the inclusion of subjects who re-treated with Tolak in the 6-12 month and overall analyses. The applicant's recurrence results are presented in Table 2. The applicant has proposed including the three recurrence rates from the first row of Table 2 in labeling in paragraph format.

Table 2 – Recurrence Assessment in Study 50 (Applicant's Results)

	0 – 6 months N=167	6 – 12 months N=153	Overall (0 – 12 months) N=184
Recurrence	70 (41.9%)	70 (45.8%)	101 (54.9%)
Non-Recurrence	97 (58.1%)	83 (54.2%)	83 (45.1%)

It is extremely difficult to interpret the applicant's analysis without a detailed understanding of the definitions regarding which subjects were included or excluded. Notably,

- Ignoring the subjects who were treated with other AK treatments between the studies or did not enroll in Study 50 decreases the denominator (number of subjects evaluated). Likely, most subjects who were treated with other treatments could be classified as subjects with a recurrence, but are not counted the numerator as potential recurrences.
- Including subjects who cleared during the interim period between the studies increases both the number of subjects classified as not having a recurrence and the denominator.
- It is confusing to include subjects who only cleared after a second round of Tolak treatment

The applicant's choices seem designed to maximize the number of subjects who can be classified as non-recurrences (including 'late responders'), and minimize the number of subjects who can be classified as recurrences (excluding those who used alternate treatments), while assuming that those who did not enroll in the study have similar outcomes to those who did enroll in the study. Thus the applicant's estimates are unreliable and may be biased in favor of increasing the estimate of the non-recurrence rate.

The applicant proposes presenting recurrence rates in three ways: 0-6 months, 6-12 months, and anytime overall. However, because Study 50 was designed to only enroll subjects who had been treated with Tolak, enrollment in Study 50 could not begin until Studies 48 and 49 were completed and unblinded. Consequently, many subjects needed to wait more than 6 months before they could enroll in Study 50. Many subjects waited 10 or 11 months before having their first visit in Study 50, and then had their 12-month visit only 1 or 2 months later, while other subjects had closer to 6 months between visits. Because of the variability in timing of the first visit, this reviewer recommends assessing for recurrence or non-recurrence across the 12-month follow-up period, rather than attempting to separate out recurrences from the two visits.

Thus, to avoid distinctions made on visit timings that are not sufficiently precise, this reviewer recommends presenting the results from Study 50 by summarizing the recurrence outcomes for the full12-month follow-up. To fully capture the best available information regarding the outcomes for all 204 subjects who were 100% clear at the end of Study 48 or 49, this reviewer recommends classifying subjects as to whether the subjects remained clear, had a recurrence or received alternate treatments, or were lost to follow-up. See Table 3.

Table 3 - Recurrence Assessment in Study 50 (Labeling Recommendation)

	N=204
Remained clear 12 months later	56 (27%)
Recurrence within 12 months or had other treatments applied	110 (54%)
No follow-up	38 (19%)

2 Introduction

2.1 Overview

NDA 22259 is a 505(b)(2) application and was originally submitted on 8/20/2007. The original application contained two Phase 3 trials (Study 48 and Study 49). Studies 48 and 49 were designed to assess the efficacy and safety of Tolak (fluorouracil) cream 4% in the treatment of actinic keratoses (AK). Study 48 had 4 arms – Tolak cream 4% (once daily (QD)), Efudex cream 5% (twice daily (BID)), vehicle cream (once daily), and comparator vehicle cream (twice daily). Study 49 had two arms – Tolak cream 4% (once daily) and vehicle cream (once daily). Efudex 5% is the listed drug for this 505(b)(2) application. The studies enrolled subjects age 18 years of age and older with at least 5 AK lesions on the face, ears, or scalp. At least 5 of the lesions were to be at least 4 mm in diameter. Lesions were to be previously untreated, clinically recognizable (palpable and/or visible to the unaided eye), clinically typical nonhypertrophic and/or nonhyperkeratotic. None of the lesions were to exceed 1 cm in size. Subjects were to apply treatment for 4 weeks. The primary efficacy endpoint was 100% complete clearance of lesions at the 4-week post-treatment visit. Both Study 48 and Study 49 demonstrated that Tolak was superior to its vehicle in the treatment of AK. The primary efficacy endpoint results for the two studies are presented in Table 4. The statistical review (dated 4/4/2008) concluded that the efficacy of Tolak cream 4% had been demonstrated in two studies. For additional details on Studies 48 and 49 refer to the original statistical review.

Table 4 – 100% Clearance Rates (Studies 48 and 49)

	Tolak 4% (QD)	Efudex 5% (BID)	Vehicle (QD)	Vehicle (BID)	p-value[a]
Study 048	N=353	N=349	N=70	N=69	
100% Clearance	192 (54%)	202 (58%)	3 (4%)	3 (4%)	<0.001
Study 049	N=50	--	N=50	--	
100% Clearance	12 (24%)		2 (4%)		0.004

[a] p-value for Tolak 4% vs. vehicle QD
Source: Statistical review dated 4/4/2008

On 6/29/2009, the applicant was issued a Complete Response letter citing deficiencies in the application related to product quality and facility inspections. The Complete Response letter did not list any issues regarding the clinical trials. Note also that nearly nine months into the original review cycle (5/7/2008), the applicant submitted an amendment containing the results of a 12-month open-label follow-up study (Study 50) assessing for recurrence, long-term safety, and retreatment in subjects treated with Tolak

in either Study 48 or 49. Although the submission included the study report, the electronic datasets were submitted in an incorrect format and could not be uploaded into the electronic document room. Due to the lateness of the amendment in the original review cycle, the lack of usable datasets, and the pending Complete Response action, Study 50 was not reviewed in the initial review cycle.

With this resubmission, the applicant has submitted information to address the product quality and facility inspection issues. The applicant has also proposed incorporating language into labeling regarding lesion recurrence rates from Study 50. As Study 50 has not previously been reviewed, this review will focus on Study 50 and the corresponding labeling.

Study 50 is an open-label long-term follow-up study for subjects treated with Tolak cream in Studies 48 and 49 to assess for recurrence, long-term safety, and the effects of re-treatment. After Studies 48 and 49 were unblinded, subjects who had been treated with Tolak were contacted regarding enrollment in Study 50. The first visit in Study 50 was to be approximately 6 months after completing Study 48/49, though for some subjects it was closer to 10 or 11 months after completing the previous study. Subjects who were clear of lesions were to return for assessment 12 months after completing the previous study. Subjects who had lesions in the treatment area during the first visit of Study 50 were offered retreatment with Tolak (once daily for 4 weeks). Subjects receiving re-treatment with Tolak in Study 50 were evaluated at the end of treatment, and 4 weeks post-treatment and 12 months after completing Study 48 or 49.

2.2 Data Sources

This reviewer evaluated the applicant's clinical study report, datasets, and proposed labeling. The submission was submitted on paper. The analysis datasets used in this review are archived at \\cdsesub4\NONECTD\NDA022259\5774834\HDFUP4LTS050\Datasets.

3 Statistical Evaluation

3.1 Data and Analysis Quality

When the study report for Study 50 was originally submitted to the application in 2008, the electronic datasets were not in the appropriate format and could not be uploaded. According to a fax generated by the Electronic Document Room staff dated 5/14/2008, the datasets were submitted as shortcuts rather than the actual files. However, the applicant did not resubmit dataset files in the appropriate format at that time, or with the current resubmission.

Thus, the Agency sent a request on 3/13/2015 for the applicant to submit the datasets in the appropriate SAS transport (.xpt) format so that the study could be reviewed. The applicant submitted .xpt format analysis datasets on 3/23/2015 which were used in this review. Although the analysis datasets were submitted in .xpt format, the raw datasets were submitted as .sas7bdat (platform-dependent SAS format) files. Even though the raw

datasets were not submitted in the requested format, the applicant's raw datasets could be loaded into statistical software programs and analyzed as needed.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study 50 is an open-label, 12-month follow-up study of subjects who were treated with Tolak in either Study 48 or Study 49. Once Studies 48 and 49 were unblinded, subjects who had received Tolak in Study 48/49 (whether or not the subject's lesions were cleared at the end of the study) were enrolled into Study 50. The first visit in Study 50 was to be at least 6 months after the 4-week post-treatment visit (primary efficacy timepoint / final visit) in Study 48/49. Subjects who had no lesions at the first follow-up visit in Study 50 were to return for an additional follow-up visit scheduled for 12 months after the final visit in Study 48/49. Subjects who had lesions at the first follow-up visit were to be treated at the discretion of the investigator—either re-treatment with Tolak or treatment with other therapies. Subjects re-treated with Tolak were evaluated at the end of treatment, 4 weeks post-treatment, and 12 months after the final visit in Study 48/49.

The protocol for Study 50 anticipated that 400 subjects would be eligible and willing to participate in the study. (Studies 48 and 49 combined enrolled a total of 403 subjects on the Tolak arm.) The protocol included plans for an interim look at the data once approximately 300 subjects were enrolled in Study 50. The applicant conducted the interim look after 310 subjects had entered Study 50 and 70 subjects completed the Month 12 visit. However, no additional subjects entered the trial after the interim look; the total enrollment of Study 50 was 310 subjects.

Reviewer comment
It does not appear that the applicant stopped enrollment after the interim analysis, as the subject with the latest end-of-study visit in Study 48/49 (12/29/2006) was enrolled in Study 50 and is included in the database. Thus it appears that the 310 subjects evaluated at the interim look include all of the subjects that the applicant was able to recruit for Study 50 from the 403 who were potentially eligible.

The initial visit in Study 50 was to occur at least 6 months after the final visit in Study 48/49. The protocol stated that subjects who were completely clear of lesions at the post-treatment (final) visit in Study 48/49 would be assessed for recurrence in Study 50.

- Subjects with no new AK lesions in the treatment areas upon entry into Study 50 were to be considered to have no recurrence and evaluated again for recurrence 12 months after the completion of Study 48/49.
- Subjects who were completely clear of lesions at the post-treatment visit in Study 48/49, but had new AK lesions in the previously treated areas upon entry into Study 50 were considered to have a recurrence.

In addition, subjects who were not completely clear of lesions at the end of Study 48/49 could be re-treated with Tolak in Study 50. Subjects who were clear of lesions 4 weeks

after this additional round of treatment would also be assessed for recurrence at the Month 12 visit.

After initial review of the data from Study 50 at the interim look (which actually ended up including first visit data for all subjects who would enroll in the study), the applicant noted that the original definition of recurrence did not adequately account for all possible scenarios. In particular, the above definitions did not provide guidance on how to deal with subjects in the following situations:

- Subjects who were treated with additional off-study therapies during the period after completing Study 48/49 but before enrolling in Study 50.
- Subjects who had lesions remaining at the end of Study 48/49, but had no lesions upon enrollment in Study 50, without the use of off-study therapies.
- Subjects who had missing lesion count data at the end of Study 48/49, but still enrolled in Study 50.

The protocol also had no discussion about how the Month 12 assessments might be utilized for subjects other than those who were clear at both the end of Study 48/49 and the first follow-up visit in Study 50 and could be further assessed for recurrence at Month 12.

Thus, after the interim review of the data, the applicant created new, more detailed definitions regarding which subjects would be included in the analyses of recurrence or non-recurrence at 6 and 12 months. The applicant's new definitions were as follows:

<u>Analysis of Recurrence at 6 Months</u>

- *Non-Recurrence:* Subjects who did not re-treat with any other medication by the 6-month evaluation and who had a lesion count of zero in the treatment areas at the 6-month evaluation (includes both subjects with no lesions at the end of Study 48/49 and subjects with lesions at the end of Study 48/49 who were clear by the 6-month follow-up visit without additional treatment).
- *Recurrence*: Subjects with no lesions at the end of Study 48/49 and who did not re-treat with any other medication by the 6-month evaluation and who had one or more lesions in the treatment area(s) at the 6-month evaluation.
- *Excluded from the analysis:*
    - Subjects who did not enroll in Study 50
    - Subjects who had missing data for the final visit in Study 48/49 (but still entered Study 50)
    - Subjects who received other treatments by the 6-month evaluation
    - Subjects who had lesions at both the end of Study 48/49 and the 6-month evaluation in Study 50

<u>Analysis of Recurrence at 12 Months</u>

- *Non-Recurrence:*
    - Subjects with no lesions at the 6-month evaluation and the 12-month evaluation and no additional treatments, OR

    - Subjects with lesions at the end of Study 48/49 and at 6 months who retreated with Tolak and were clear at the 4-week post-treatment visit and the 12 month visit.
- *Recurrence*:
    - Subjects with no lesions at the 6-month evaluation and with one or more lesions at the 12-month evaluation, OR
    - Subjects with no lesions at the end of Study 48/49 but with lesions at the 6-month evaluation who received re-treatment with Tolak or no treatment (regardless of whether or not the lesions cleared at the end of re-treatment or were present at the 12-month evaluation) OR
    - Subjects with lesions at both the end of Study 48/49 and the 6-month evaluation who received re-treatment with Tolak or no treatment and had lesions present at the 12-month evaluation.
- *Excluded from the analysis:*
    - Subjects who did not enroll in Study 50
    - Subjects who did not return for the 4-week post-treatment visit in Study 48/49 (but still entered Study 50)
    - Subjects who received other treatments by the 6-month or 12-month evaluation
    - Subjects who had lesions remaining after re-treatment with study medication or no treatment in Study 50 (among subjects with lesions at both the end of Study 48/49 and the 6-month evaluation)

The applicant also defined an overall recurrence rate which counted all subjects who recurred at any time during the 12 month study period. This calculation was similar to the 12-month calculation, except that subjects counted as recurrences at Month 6 who then received other treatment other than Tolak were counted as recurrences rather than as excluded from the analysis.

Reviewer Comment
The protocol's original intention was to follow Tolak-treated subjects who were completely clear of lesions at the post-treatment visit in Study 48/49 for recurrence. However, the applicant's new definitions increase the number of subjects who did not have a recurrence by including subjects who were not clear at the end of the previous study, but who were able to achieve clearance by the time the subjects were entered into Study 50 without additional treatment. The population evaluated at the 12-month visit also includes subjects who achieved clearance only after the second round of treatment in Study 50, and were not clear at the end of Study 48/49. Thus they are no longer following just the group of subjects identified as responders in Study 48/49.

Additionally, the applicant has systematically excluded two key groups of subjects from the analysis—subjects who did not enroll in Study 50, and subjects who used alternate treatments at any time after the end of Study 48/49. The subjects who used alternate AK treatments prior to enrolling in Study 50 should not be systematically ignored, as these subjects are actually presenting strong evidence that they may have had a recurrence.

Any data summaries should also account for the subjects who were lost to follow-up and did not enroll in Study 50.

Thus, this reviewer recommends following the original intention of the protocol for assessing recurrence among the subjects who were clear at the end of the pivotal trials, rather than using the definitions that were crafted after the interim look at the data. This reviewer recommends tabulating the best available information on all subjects who received Tolak treatment and achieved complete clearance of lesions at the post-treatment visit in Study 48/49: recurrence by Month 12, non-recurrence by Month 12, additional treatments utilized, or data missing.

3.2.2 Study Subjects

Studies 48 and 49 randomized 403 subjects to the Tolak arm (353 subjects in Study 48 and 50 subjects in Study 49). Of these subjects, 203 were observed to be completely clear of lesions 4 weeks post-treatment and 1 subject was imputed to be completely clear using LOCF, for a total of 204 subjects classified as responders. Of the remaining subjects, 183 were observed post-treatment to have lesions remaining and 16 subjects were imputed using LOCF to have lesions remaining for a total of 199 subjects classified as non-responders. Approximately 81% of subjects who completely cleared of lesions at the end of Study 48/49 enrolled in Study 50, while approximately 72% of subjects who did not completely clear of lesions at the end of Study 48/49 enrolled in Study 50. Three subjects who did not have and end of study visit in Study 48/49 enrolled into Study 50. See Table 5.

Table 5 – Subject Enrollment in Study 50

	Status in Study 50	
Status at End of Study 48/49	Enrolled	Did not enroll
Completely Clear (N=204)		
Observed	166 (81%)	37 (18%)
Imputed	0	1 (<1%)
Lesions Remaining (N=199)		
Observed	141 (71%)	42 (21%)
Imputed	3 (2%)	13 (7%)

Source: reviewer analysis.

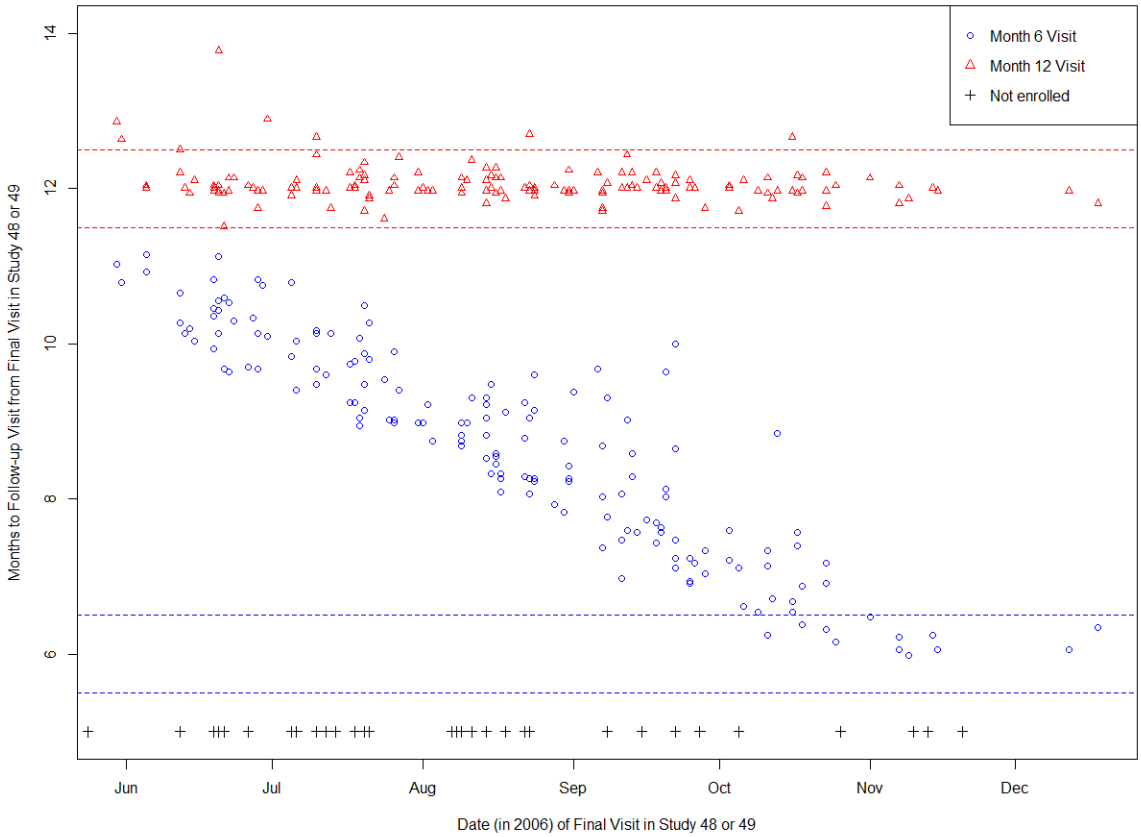
3.2.3 Timing of Assessments

The intention of Study 50 was to assess subjects 6 months and 12 months after the completion of Study 48/49 (with additional visits for subjects who were re-treating with Tolak). However, because Study 50 only enrolled subjects who had received Tolak in Study 48/49, enrollment could not begin until Studies 48 and 49 were unblinded. Consequently, those subjects who completed Study 48/49 the earliest generally had to wait more than 6 months before enrollment in Study 50 opened. Some subjects had their '6-month' evaluation as long as 11 months after completing Study 48/49. Nonetheless, the '12-month' evaluation was to be scheduled as close as possible to 12 months after completing Study 48/49, regardless of when the '6-month' evaluation occurred. Among the subjects who were completely cleared at the end of Study 48/49 and entered Study 50,

only 7% (12/166) of subjects had their '6-month' evaluation within a nominal 6 ± 0.5 month window. Most subjects, however, did have their '12-month'evaluation within a nominal 12 ± 0.5 month window. The correlation between the date of completion of Study 48/49 and the number of months between the end of Study 48/49 and entry in Study 50 can be seen in Figure 1, with the subjects who completed Study 48/49 earlier having longer wait times before enrollment in Study 50 than those who completed Study 48/49 later.

Reviewer Comment
Because the '6-month' evaluation was frequently conducted much later than 6 months after the previous study completion, it may not make much sense to make a distinction between subjects who had recurrences observed at the first follow-up visit and those who had recurrences observed at the second follow-up visit, as the two visits could be anywhere from 1 to 6 months apart. Therefore this reviewer recommends reporting whether subjects had recurrence by Month 12 or remained clear through 12 months of follow-up, rather than distinguishing between whether the recurrences were observed at the first follow-up visit or the second. The variable name (6-month evaluation) implies a greater precision in timing than could be achieved in practice.

Figure 1 – Timing of Month 6 Evaluation and Month 12 Evaluation Relative to Date of Final Visit in Study 48 or 49



Source: reviewer analysis.

3.2.4 Recurrence Results

The applicant defined three recurrence analyses, labeled as 0-6 months, 6-12 months, and overall (0-12 months). The protocol did not include clear definitions regarding which subjects should be included in the numerator or denominator for recurrence estimates, and each of the three analyses defined different denominators. All of the applicant's analyses excluded subjects who did not enroll in Study 50, those who did not attend the end of study visit in Study 48/49, and those who used other treatments between the two studies. The outcomes in Study 50 of the 403 subjects who received Tolak in Study 48/49 are displayed in Figure 2.

For the 0-6 month analysis, the denominator was defined by subjects who either (1) had no lesions at the end of Study 48/49, or (2) had no lesions at the beginning of Study 50 (among subjects who enrolled in Study 50 and did not use other treatments). A subject is considered to have a recurrence if they had no lesions at the end of Study 48/49 but did have lesions at the first follow-up visit in Study 50. These subjects are labeled in Figure 2 with Y_1. A subject is considered to have no recurrence (1) if they had no lesions at the end of Study 48/49 and no lesions at the first follow-up visit in Study 50, or (2) they had lesions at the end of Study 48/49 but no lesions at the first follow-up visit in Study 50 (and did not report using treatments outside the study). These subjects are labeled in Figure 2 as N_1.

For the 6-12 month analysis, in addition to excluding subjects who did not enroll in Study 50 or subjects who used other treatments between the studies, the denominator also excludes subjects who were counted as recurrences in the first analysis but used other treatments (not Tolak) on their lesions after entering into Study 50. In addition, the group of subjects who had lesions at both the end of Study 48/49 and the beginning of Study 50 and were re-treated with Tolak (or no treatment) during Study 50 and cleared of their lesions 4 weeks post-treatment are now included in the denominator. A subject is considered to have a recurrence (1) if they had no lesions at the beginning of Study 50 (6-month evaluation), but had lesions at the Month 12 visit, or (2) if they had no lesions at the end of Study 48/49, but did have lesions at the beginning of Study 50, and re-treated with Tolak or had no treatment (whether or not the lesions cleared with retreatment or were present at Month 12), or (3) if they had lesions at the end of Study 48/49 and at the beginning of Study 50, re-treated with Tolak or had no treatment, cleared of lesions 4 weeks post-treatment, and had lesions present at Month 12. These subjects are labeled in Figure 2 with Y_2. A subject is considered to have no recurrence if (1) they had no lesions at the beginning of Study 50 (6-month evaluation) and no lesions at the Month 12 visit, or (2) they had lesions at the end of Study 48/49 and the beginning of Study 50, re-treated with Tolak or no treatment, cleared of lesions 4 weeks post-treatment, and were still clear at the Month 12 visit. These subjects are labeled in Figure 2 with N_2.

The 0-12 month overall analysis is almost identical to the 6-12 month analysis, except that one group of subjects (those who had no lesions at the end of Study 48/49, but had a recurrence upon entry into Study 50 and were treated with other treatments rather than Tolak) were counted as subjects with recurrence rather than excluded from the analysis (due to using other treatments). The subjects included in this analysis are labeled in

Figure 2 with N_2, Y_2, and Y_O. The applicant's recurrence rates for the three analyses are presented in Table 6.

Table 6 – Recurrence Assessment in Study 50 (Applicant's Results)

	0 – 6 months N=167	6 – 12 months N=153	Overall (0 – 12 months) N=184
Recurrence	70 (41.9%)	70 (45.8%)	101 (54.9%)
Non-Recurrence	97 (58.1%)	83 (54.2%)	83 (45.1%)

Source: pg 34 of the Study 50 study report.

Reviewer Comment

(b) (4)

Because these estimates ignore subjects who used other treatments (a likely indicator of recurrence) or did not enroll in Study 50, and also include some subjects who had lesions at the end of Study 48/49 or had re-treatment with Tolak, the estimates do not represent an intuitive estimate of recurrence.

Instead, this reviewer recommends presenting the follow-up outcomes for the 204 subjects with complete clearance in Study 48/49 as presented in Figure 3 (remain clear, recurrence, applied other treatments, no follow-up). The outcomes in Figure 3 are summarized in Table 7. This table separates out the 6-month evaluation and 12-month evaluation, as well as distinguishes subjects who reported using other treatments between studies from subjects who had lesions present.

Table 7 - Recurrence Assessment in Study 50 (Reviewer's Results)

	N=204
Remained clear at 1st follow-up visit[a]	75 (37%)
Remained clear at 2nd follow-up visit[b]	56 (27%)
Recurrence at 2nd follow-up visit[b]	19 (9%)
Recurrence at 1st follow-up visit[a]	70 (34%)
Other treatments applied by 1st follow-up visit[a]	21 (10%)
No follow-up/ Outcome unknown	38 (19%)

[a] 6-11 months after completing Study 48/49

[b] 12 months after completing Study 48/49

Source: reviewer analysis.

Because of the lack of precision of the timing of the first visit in Study 50 (subjects were first assessed between 6 and 11 months after the end of the previous study, and in some subjects the 12-month visit was only 1 month after the first visit), and fact that the subjects who applied other treatments for AK have strong evidence of recurrence, the following simplified table is recommended to convey the findings of Study 50 in labeling (Table 8).

Table 8 - Recurrence Assessment in Study 50 (Labeling Recommendation)

	N=204
Remained clear 12 months later	56 (27%)
Recurrence within 12 months or had other treatments applied	110 (54%)
No follow-up	38 (19%)

Source: reviewer analysis.

Figure 2 - Applicant's Recurrence Classifications in Study 50 (page 1 of 2)

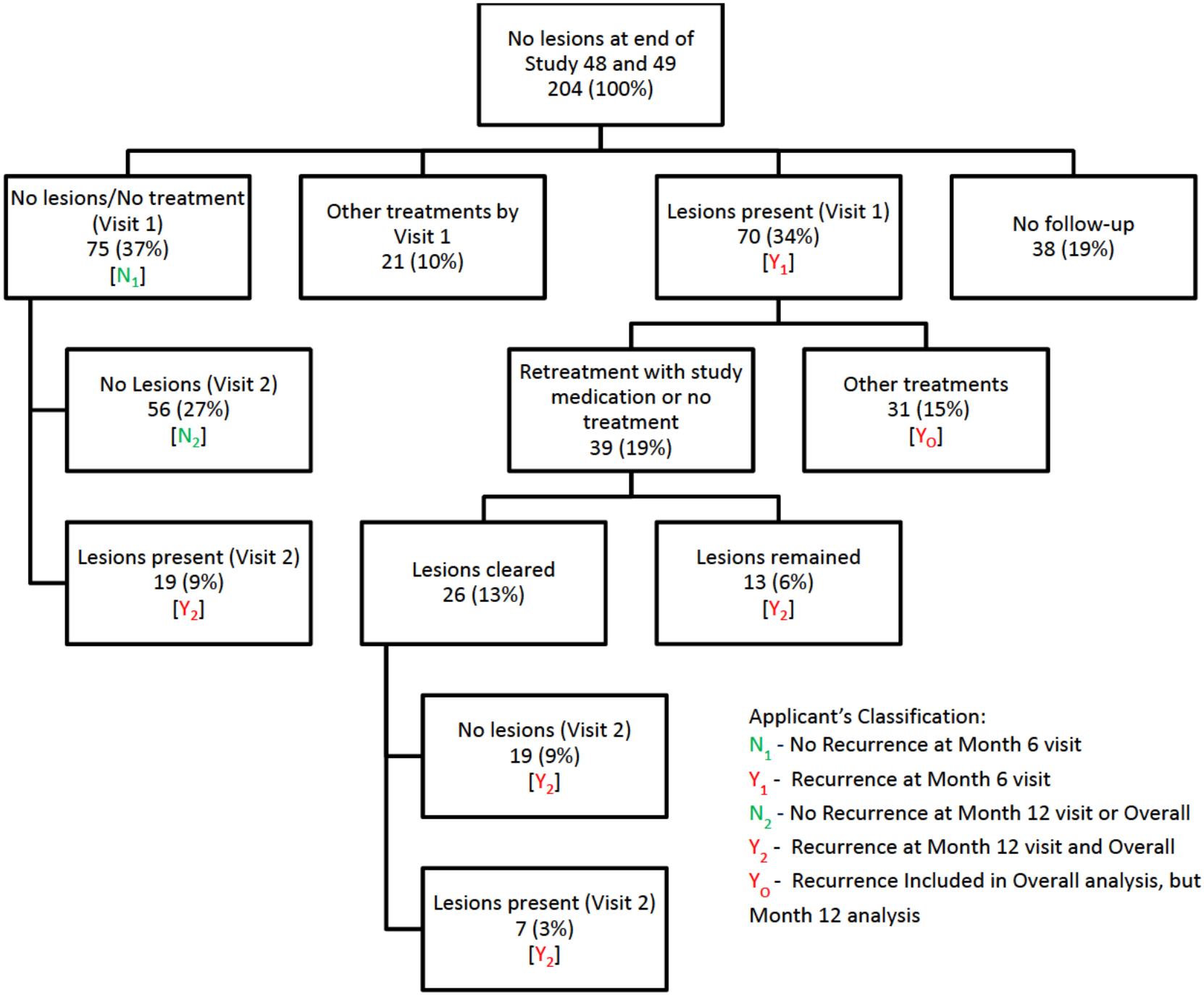


Figure 2 - Applicant's Recurrence Classifications in Study 50 (page 2 of 2)

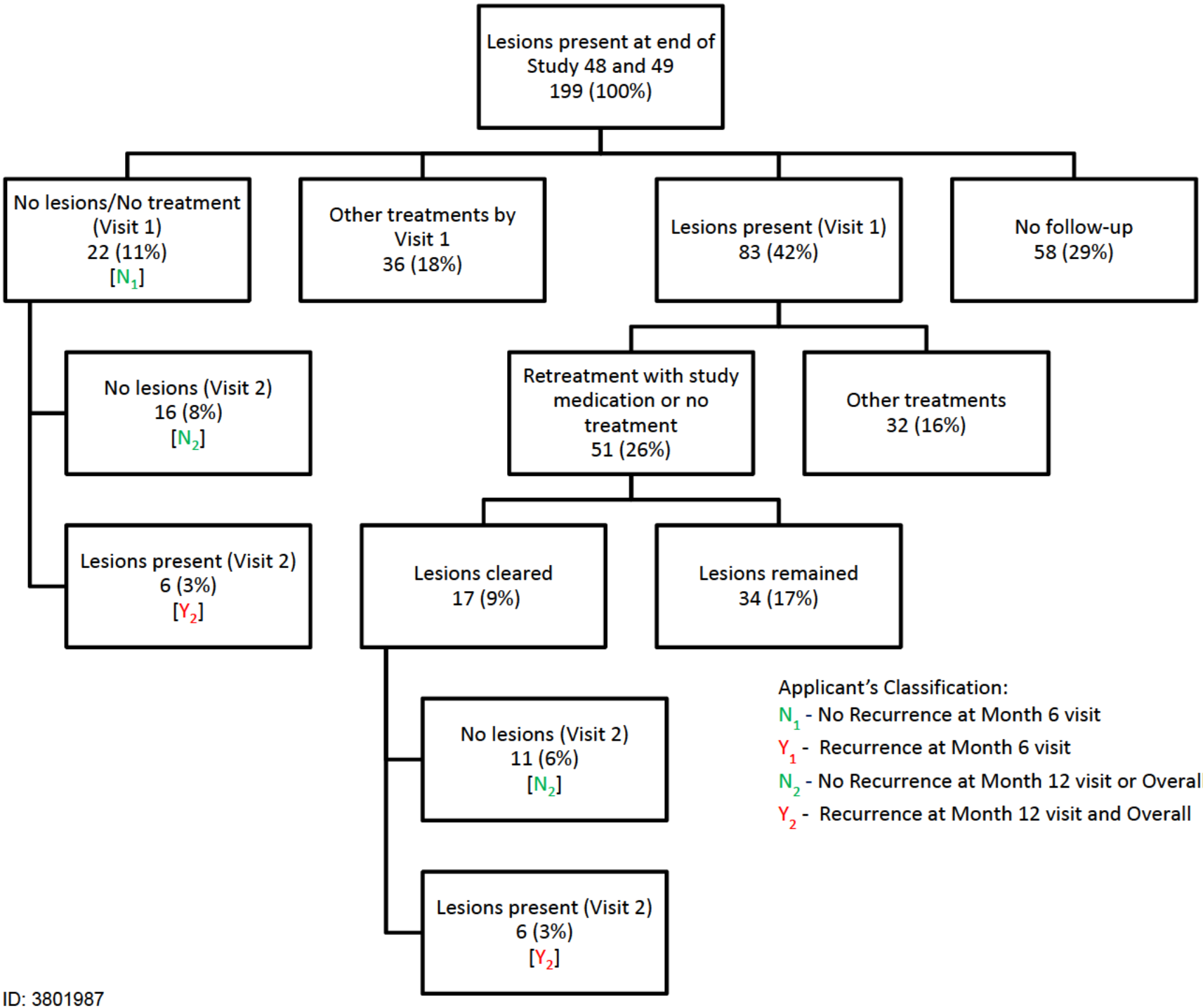
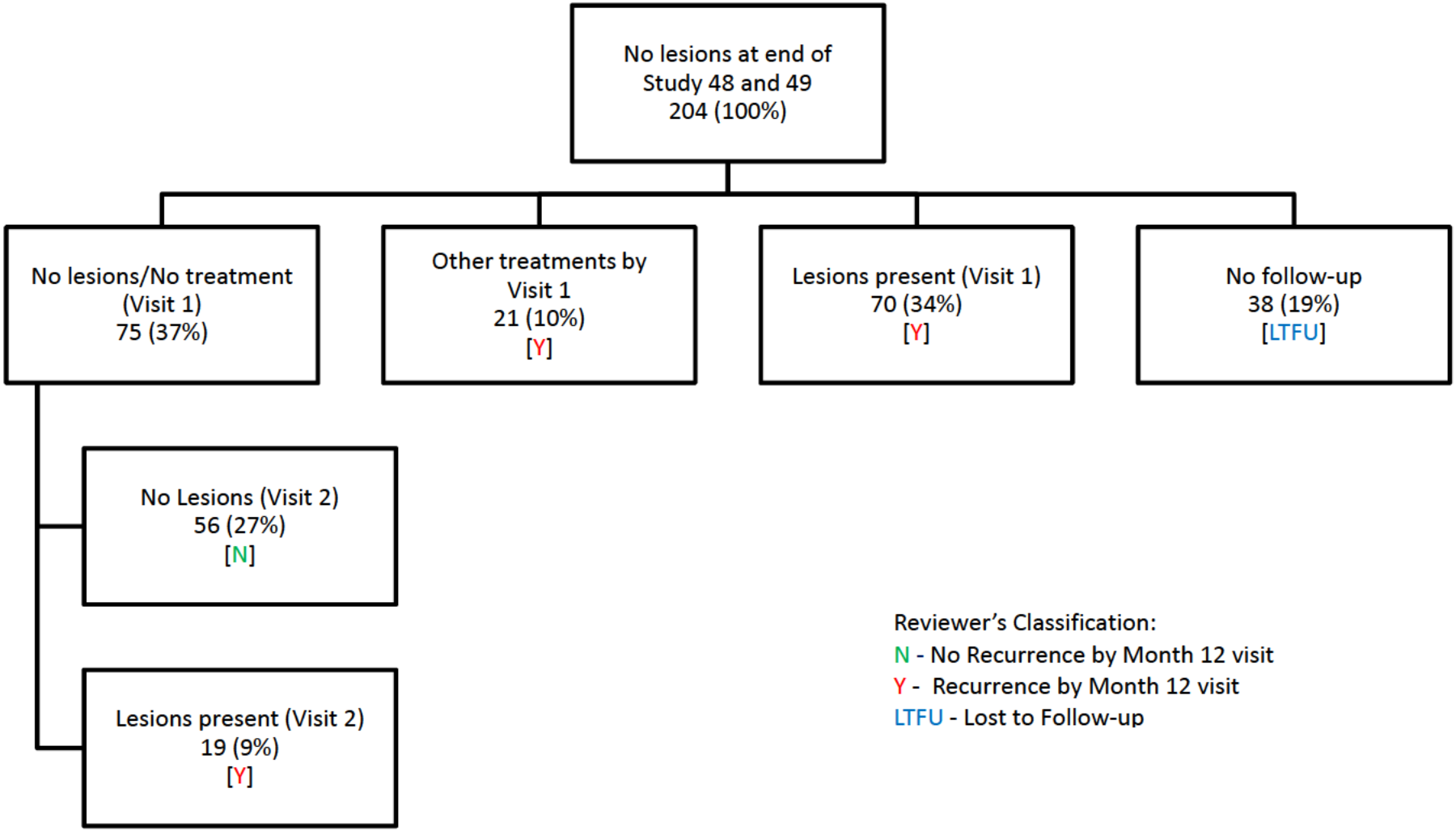


Figure 3 - Reviewer's Recurrence Classifications



3.3 Evaluation of Safety

Refer to the clinical review.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, Age, and Geographic Region

Study 50 was an open-label follow-up study to estimate recurrence rates. As the study did not include hypothesis testing, subgroup analyses were not conducted.

4.2 Other Special/Subgroup Populations

Not applicable.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The original statistical review of this application (dated 4/4/2008) concluded that the efficacy of Tolak cream 4% had been demonstrated in Studies 48 and 49. For this resubmission, this review evaluated the long-term follow-up data collected in Study 50, which was not complete at the time of the original NDA submission. Study 50 enrolled subjects who had been treated with Tolak in Study 48/49 and evaluated them twice—at least 6 months after completing Study 48/49 and 12 months after completing Study 48/49. Subjects who cleared were evaluated for recurrence, and subjects with lesions were offered re-treatment with Tolak or alternate therapies.

The protocol for Study 50 did not include comprehensive definitions for how recurrence or non-recurrence would be defined, stating only that

- Subjects with no new AK lesions in the treatment areas upon entry into Study 50 were to be considered to have no recurrence and evaluated again for recurrence 12 months after the completion of Study 48/49.
- Subjects who were completely clear of lesions at the post-treatment visit in Study 48/49, but had new AK lesions in the previously treated areas upon entry into Study 50 were considered to have a recurrence.
- Subjects who were not completely clear of lesions at the end of Study 48/49 could be re-treated with Tolak in Study 50. Subjects who were clear of lesions 4 weeks after this additional round of treatment would be assessed for recurrence at the Month 12 visit.

After looking at the data at the interim analysis (which included the first visit data for all subjects who enrolled in the study) the applicant defined additional groups of subjects who should be either included or excluded from the recurrence and non-recurrence definitions. For example, subjects who were not clear at the end of Study 48/49 but were clear by the entry into Study 50 could be followed for recurrence and subjects who used alternate treatments between the completion of Study 48/49 and the start of Study 50 were excluded from the analysis. Thus, the applicant's recurrence rates lose the

connection to the subjects classified as responders at the end of Study 48/49 (some subjects are excluded from the recurrence analysis for using other treatments), while other subjects are added to the analysis (those who cleared after the end of Study 48/49 and those who re-treated with Tolak during Study 50). In particular, ignoring the subjects who treated with other AK treatments between the studies loses important information about potential recurrences in these subjects. The natural population to assess for recurrence is the subjects who were clear at the end of Study 48/49, and the analysis data presentation should account for the best available information on all of the cleared subjects.

Because Study 50 only enrolled subjects who had been treated with Tolak in Study 48/49, enrollment in Study 50 could not begin until Studies 48 and 49 were unblinded. Consequently, many subjects needed to wait more than 6 months before they could enroll in Study 50. Many subjects waited 10 or 11 months before having their first visit in Study 50, and then had their second visit only 1 or 2 months later at Month 12, while other subjects had closer to 6 months between visits. Because of the variability in timing of the first visit, it makes sense to assess for recurrence or non-recurrence across the 12-month follow-up period, rather than attempting to separate out recurrences from the two visits.

5.2 Conclusions and Recommendations

The original application for NDA 22259 (submitted on 8/20/2007) contained two Phase 3 trials (Study 48 and Study 49). Studies 48 and 49 were designed to assess the efficacy and safety of Tolak (fluorouracil) cream 4% in the treatment of actinic keratoses (AK). Both Study 48 and Study 49 demonstrated that Tolak was superior to its vehicle in the treatment of AK. The original statistical review (dated 4/4/2008) concluded that the efficacy of Tolak cream 4% had been demonstrated in two studies. For this review, the conclusion that the efficacy of Tolak in the treatment of AK has been demonstrated in studies remains the same.

In this resubmission, the applicant has updated their proposed labeling to include the results of a 12-month follow-up study (Study 50) assessing for recurrence and the effects of re-treatment in subjects treated with Tolak in either Study 48 or 49. The applicant has proposed including the following language in labeling regarding long-term follow-up and recurrence, using their definitions of recurrence for the 0-6 month, 6-12 month, and overall analyses:

(b) (4)

However, the applicant's definitions seem designed to maximize the number of subjects who can be classified as non-recurrences (including 'late responders'), and minimize the

number of subjects who can be classified as recurrences (excluding those who used alternate treatments), while assuming that those who didn't enroll in the study have similar outcomes to those who did enroll in the study. Thus the applicant's estimates are unreliable and may be biased in favor of increasing the estimate of the non-recurrence rate.

In addition, there was a lot of variability in the timing of the subjects' first visit in Study 50, with many subjects having their first follow-up visit 10 or 11 months after completing Study 48/49 rather than the nominal 6 months. Because of the variability in timing of the first visit, this reviewer recommends assessing for recurrence or non-recurrence across the 12-month follow-up period, rather than attempting to separate out recurrences from the two visits.

Therefore, this reviewer recommends presenting the results from Study 50 by summarizing the 12-month follow-up outcomes for all subjects who were 100% clear at the end of Study 48 or 49 as to whether the subject remained clear, had a recurrence or received alternate treatments, or was lost to follow-up.

Table 9 - Recurrence Assessment in Study 50 (Labeling Recommendation)

	N=204
Remained clear 12 months later	56 (27%)
Recurrence within 12 months or had other treatments applied	110 (54%)
No follow-up	38 (19%)

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, Ph.D.
Date: 8/5/2015

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
DDDP/Marcus
DDDP/Kettl
DDDP/Woitach
DDDP/Dixon
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Fritsch

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHLEEN S FRITSCH
08/05/2015

MOHAMED A ALOSH
08/05/2015

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

NDA/Serial Number:	22-259 / N-000
Drug Name:	TRADENAME (5-fluorouracil) cream 4%
Indication(s):	Actinic Keratoses
Applicant:	Hill Dermaceuticals
Dates:	Submitted: 8/20/2007 PDUFA: 6/20/2008
Review Priority:	Standard review
Biometrics Division:	Division of Biometrics III
Statistics Reviewer:	Kathleen Fritsch, PhD
Concurring Reviewer:	Mohamed Alosh, PhD
Medical Division:	Division of Dermatology and Dental Products
Clinical Team:	David Kettl, MD / Markham Luke MD, PhD
Project Manager:	Catherine Carr

Keywords: actinic keratoses, 505(b)(2)

Table of Contents

1 Executive Summary

1.1 Conclusions and Recommendations

Tradename (5-fluorouracil) cream 4% was superior to its vehicle in the treatment of actinic keratoses in two studies. Tradename (5-fluorouracil) cream 4% (referred to as 4% 5-FU) was applied once daily for 4 weeks by subjects with at least 5 actinic keratoses on the face, scalp, or ears. The primary efficacy endpoint was 100% clearance of lesions 4 weeks post-treatment. This application was submitted under Section 505(b)(2) with Efudex (5-fluorouracil) cream 5% as the listed drug. The treatment regimen for Tradename cream differs from Efudex in the drug concentration (4% vs. 5%), frequency of use (once daily vs. twice daily), and in the composition of the vehicle. The sponsor conducted two concurrent studies. Study 048 was a four-arm study comparing 4% 5-FU once daily, Efudex cream 5% twice daily, test product vehicle once daily, and comparator vehicle twice daily. Study 049 was a two-arm study comparing 4% 5-FU once daily and test product vehicle once daily. The efficacy results for the 100% clearance rate 4 weeks post-treatment are presented in Table 1. The efficacy of 4% 5-FU is supported by the demonstration that the test product is superior to its vehicle in two studies. The test product was not shown to be non-inferior to the listed drug Efudex (97.5% lower confidence bounds of -11.1% (ITT) and -12.8% (PP) with a pre-specified non-inferiority margin of 10%) in Study 048.

Table 1 – 100% Clearance Rates (Studies 048 and 049 – ITT)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Study 048	N=353	N=349	N=70	N=69
100% Clearance	192 (54%)	202 (58%)	3 (4%)	3 (4%)
p-value / LCB		-11.1%[a] -12.8%[b]	<0.001[c]	
Study 049	N=50	--	N=50	--
100% Clearance	12 (24%)		2 (4%)	
p-value			0.004[c]	

[a] 97.5% ITT lower confidence bound for the difference between 4% 5-FU and Efudex
[b] 97.5% PP lower confidence bound for the difference between 4% 5-FU and Efudex
[c] p-value for 4% 5-FU vs. vehicle QD

1.2 Brief Overview of Clinical Studies

Tradename (5-fluorouracil) cream 4% has been submitted as a 505(b)(2) application for the treatment of actinic keratoses. The reference drug is Efudex (5-fluorouracil) cream 5%. The sponsor's development plan included a Phase 2 dose ranging study (045), two Phase 3 studies, one large study with the goal of establishing the superiority of 4% 5-FU to its vehicle and the non-inferiority of 4% 5-FU to Efudex (048) and one small study with the goal of establishing the superiority of 4% 5-FU to its vehicle (049). Although Study 048 was designed to assess the non-inferiority of 4% 5-FU to Efudex, the sponsor considered the fact that it might be difficult to establish the non-inferiority, and designed the clinical program from the start to include a second vehicle-controlled Phase 3 study. The Agency agreed with the plan to conduct two Phase 3 studies (one 4-arm and one 2-

arm) and both Phase 3 studies were simultaneously reviewed under Special Protocol Assessments (letter date 2/16/2006). The primary efficacy endpoint was 100% clearance of lesions 4 weeks post-treatment. The studies had two secondary endpoints, 75% clearance of lesions at the 4 weeks post-treatment visit and the percent change from baseline in the number of lesions. Features of the clinical studies are presented in Table 2. All studies were conducted in the U.S. The Phase 2 dose ranging study (045) is not further discussed in this review.

Table 2 – Clinical Study Program for 4% 5-FU Cream

Study	Treatment Arms	No. of Subjects	Study Dates
HD-FUDR-045	5-FU Cream 4% (QD 4 Wks)	20	April – September 2005
	5-FU Cream 4% (BID 4 Wks)	20	
	5-FU Cream 4% (QD 2 Wks)	20	
	5-FU Cream 4% (BID 2 Wks)	21	
	Vehicle Cream (BID 4 Wks)	20	
	Efudex Cream 5% (BID 4 Wks)	20	
HD-FUP3B-048	5-FU Cream 4% (QD)	353	March – December 2006
	Efudex Cream 5% (BID)	349	
	Vehicle Cream (QD)	70	
	Compartor Vehicle Cream (BID)	69	
HD-FUP3B-049	5-FU Cream 4% (QD)	50	May – October 2006
	Vehicle Cream (QD)	50	

1.3 Statistical Issues and Findings

Tradename (5-FU) 4% was superior to vehicle in both Phase 3 studies for the primary efficacy endpoint of 100% clearance of actinic keratoses at 4 weeks post-treatment. However, the treatment effect for 4% 5-FU versus vehicle for the clearance rate was much higher in Study 048 than 049 (Study 048: 54% vs. 4%; Study 049: 24% vs. 4%). The reason for this difference is not clear, though it does not appear to be explained solely by differences in precision afforded by the respective sample sizes (Study 048 enrolled 353 4% 5-FU subjects while Study 049 enrolled 50 4% 5-FU subjects), or by differences in baseline lesion count (mean of 19.2 for Study 049 vs. 14.4 for Study 048 for 4% 5-FU subjects). Tradename (5-FU) 4% was also superior to vehicle in both studies for the secondary endpoints of 75% reduction in lesions and percent reduction in lesions. Study 048 was not able to demonstrate that 4% 5-FU was non-inferior to Efudex as the 97.5% lower confidence bounds for the treatment difference were -11.1% (ITT) and -12.8% (PP) when the pre-specified non-inferiority margin was 10%.

For subjects treated with 5-FU, lesion counts typically increased during the 4-week treatment period before resolving during the post-treatment period. In some subjects the increase could be many-fold (up to 2000% increase). Subjects who discontinued the study early from the 5-FU arms often had counts carried forward in the analysis that were higher than baseline. Since 5-FU subjects tend to worsen before they get better and many 5-FU subjects improved post-treatment even if they did not complete a full course of treatment, while vehicle subjects tended to remain stable around their baseline values

during and post-treatment, an LOCF analysis appears to be a fairly conservative way of handling missing data.

Many 5-FU subjects could not be assessed for lesion counts during treatment either due to skin reactions such as erythema or inflammation, or because the lesions were too numerous to count. Approximately 1/4 of 4% 5-FU subjects in Study 048 and 1/2 of 4% 5-FU subjects in Study 049 did not have lesion counts done at Week 4 due to such reasons, even though they attended the visit. Lesion counts for vehicle subjects were typically stable during the treatment and post-treatment periods. Most 5-FU subjects experienced adverse events during the treatment period such as erythema (99%), scaling/dryness (95%), crusting (87%), pruritus (85%), stinging/burning (87%), edema (69%), and erosions (68%). These events were actively assessed during treatment. Many of these events were severe.

2 Introduction

2.1 Overview

Tradename (5-fluorouracil) cream 4% has been submitted as a 505(b)(2) application for the treatment of actinic keratoses. The reference drug is Efudex (5-fluorouracil) cream 5%. The treatment regimen for Tradename cream differs from Efudex in the drug concentration (4% vs. 5%), frequency of use (once daily vs. twice daily), and in the composition of the vehicle. The sponsor conducted two Phase 3 studies. Study HD-FUP3B-048 was a randomized, evaluator blinded, four-arm study of 4% 5-FU once daily, vehicle once daily, Efudex cream 5% twice daily, and a comparator vehicle cream twice daily. The study enrolled 841 subjects (353 to 4% 5-FU, 349 to Efudex, 70 to vehicle once daily, and 69 to vehicle twice daily) at 26 U.S. centers. The study goals were to establish the superiority of 4% 5-FU to its vehicle and the non-inferiority of 4% 5-FU to Efudex. Study 048 was conducted from March 30, 2006 to December 29, 2006. The second study, Study HD-FUP3B-049 was a randomized, double-blind, two-arm study of 4% 5-FU once daily and vehicle once daily. The study enrolled 100 subjects (50 to 4% 5-FU and 50 to vehicle) at 5 U.S. centers. Study 049 was conducted from May 22, 2006 to October 17, 2006.

To establish the efficacy of a drug product submitted as a 505(b)(2) application, a sponsor can either submit adequate data on the test product to support efficacy (typically from two vehicle-controlled studies) or build a clinical bridge to the Agency's findings of efficacy from the reference product. For topical products this is often done by conducting a 3-arm study demonstrating that the test product is superior to its vehicle and non-inferior to the reference product. For this application the sponsor elected to conduct two studies, one large study with the goal of establishing the superiority of 4% 5-FU to its vehicle and the non-inferiority of 4% 5-FU to Efudex and one small study with the goal of establishing the superiority of 4% 5-FU to its vehicle. Thus, if the large study was unable to demonstrate the non-inferiority of the test product to the reference product, then the sponsor had the ability to demonstrate that the test product was superior to vehicle in two studies.

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in CTD format on paper with electronic datasets. The datasets used in this review are archived at \\cdsesub1\ nonectd\N22259\2007-08-17.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study HD-FUP3B-048 was a randomized, evaluator blinded, four-arm study of 5-fluorouracil (5-FU) cream 4% once daily, vehicle once daily, Efudex cream 5% twice daily, and comparator vehicle cream twice daily. Subjects were 18 years of age or older and had at least 5 actinic keratosis (AK) lesions on the face, ears, or scalp. At least 5 of the lesions were to be at least 4 mm in diameter. Lesions were to be previously untreated, clinically recognizable (palpable and/or visible to the unaided eye), clinically typical nonhypertrophic and/or nonhyperkeratotic. None of the lesions were to exceed 1 cm in size. Subjects were to apply treatment for 4 weeks, either once daily (4% 5-FU and vehicle) or twice daily (Efudex and comparator vehicle). The investigator was blinded to treatment frequency (once daily or twice daily). Someone other than the investigator was responsible for dispensing treatment, providing instructions for use, and weighing tubes. However, the same investigator was responsible for efficacy and safety evaluations. Subjects were evaluated at baseline, Week 1, Week 2, Week 4, 2 weeks post-treatment, and 4 weeks post-treatment. Subjects who discontinued the treatment phase early were to be entered into the follow-up phase of the study.

The primary efficacy endpoint was 100% clearance of lesions at the 4 weeks post-treatment visit. The protocol specified two secondary endpoints, 75% clearance of lesions at the 4 weeks post-treatment visit and the percent change from baseline in the number of lesions. The primary comparisons were to demonstrate the non-inferiority of 4% 5-FU to Efudex and to demonstrate the superiority of 4% 5-FU to its vehicle. The non-inferiority comparison was to be evaluated with a 97.5% one-sided confidence interval using Wald's confidence interval with Yate's continuity correction and a 10% non-inferiority margin on the ITT and per protocol populations. The superiority comparison was to be evaluated with a Cochran-Mantel-Haenszel test stratified on center. The proportion of subjects with a 75% reduction in lesions was to be analyzed in the same way as the primary endpoint. The percent change in lesions was to be analyzed with an analysis of variance with factors for treatment and center. If the Wilk-Shapiro test for normality were significant at 0.01, then the analysis would be conducted on rank-transformed data. Centers enrolling fewer than 10 subjects per active treatment arm and 2 subjects per vehicle arm in Study 048 or centers enrolling fewer than 8 subjects per treatment arm in Study 049 were pooled pairwise for the analyses (largest under-enrolling center pooled with the smallest under-enrolling center, etc. until minimums are met).

The ITT population was defined as all subjects randomized and dispensed medication. The per protocol population excluded subjects who did not meet the inclusion criteria (specifically with regard to lesion requirements), subjects who used interfering concomitant medications, subjects who did not complete the Week 4 end-of-treatment visit and the 4 weeks post-treatment visit, subjects whose 4 weeks post-treatment visit was not within the visit window of ± 5 days, subjects who missed more than one interim visit (Week 1, Week 2, or 2 weeks post-treatment), and subjects who did not apply 80% to 120% of expected treatment applications.

Study HD-FUP3B-049 had the same inclusion criteria and design, except that it was a two-arm study with the goal of demonstrating that 4% 5-FU once daily was superior to its vehicle.

3.1.2 Subject Disposition

The number of subjects discontinuing the study was similar across treatment arms in Studies 048 and 049 and ranged from 4% to 10%. The most common reason for subject dropout was subject decision. The reasons for study discontinuation are presented in Table 3 and Table 4. One subject in Study 049 (treated with 4% 5-FU) died during the study. This subject was an 82 year old male who died of a heart attack one day after completing the 4-week treatment period of the study. The investigator considered the event unrelated to study medication.

Table 3 – Subjects Discontinuing Study (Study 048)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects who Discontinued Study	13 (4%)	20 (6%)	3 (4%)	7 (10%)
Adverse Event	2 (Sepsis, Burning/Stinging)	2 (Cracked Femur, Skin Reaction)	1 (Knee fracture)	-
Lost to Follow-Up	2	3	-	1
Noncompliance	-	2	-	-
Subject's Decision	9	12	2	6
Other	-	1 (Husb. in Hosp.)	-	-

Table 4 – Subjects Discontinuing Study (Study 049)

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects who Discontinued Study	4 (8%)	4 (8%)
Adverse Event	-	2 (Dermatitis, Syncope)
Lost to Follow-Up	1	-
Noncompliance	1	-
Subject's Decision	1	-
Other	1 (Death)	2 (Out of Town [2])

Besides the subjects who prematurely discontinued the study, other subjects terminated the treatment phase early, but returned for the 4 week follow-up visit. The cross-tabulations of subjects completing treatment (yes/no) and completing the study (yes/no) are presented in Table 5 and Table 6. For the 5-FU arms, the adverse events leading to treatment discontinuation were nearly always local skin reactions like erythema, burning, stinging, crusting, pain, or pruritus. The breakdown of reasons subjects discontinued treatment (whether or not they completed follow-up) are presented in Table 7 and Table 8. The number of cases where the reason for stopping treatment could be classified as a local adverse reaction (whether the reason was listed as an adverse event, subject decision, or other) is also noted. These cases were classified by this reviewer based on the verbatim reasons for discontinuing. In Study 048, 39/353 (11%) of 4% 5-FU subjects and 59/349 (17%) of Efudex subjects terminated treatment early due to local adverse reactions. In Study 049, 11/50 (22%) of 4% 5-FU subjects terminated treatment early due to local adverse reactions. No vehicle subjects discontinued treatment due to local adverse reactions.

Table 5 – Number of Subjects Completing Treatment and/or Follow-up (Study 048)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects Completing Treatment	306 (87%)	270 (77%)	68 (97%)	63 (91%)
Subjects who Completed Study	304	269	66	62
Subjects who Discontinued Study	2	1	2	1
Subjects Discontinuing Treatment	47 (13%)	79 (23%)	2 (3%)	6 (9%)
Subjects who Completed Study	36	60	1	0
Subjects who Discontinued Study	11	19	1	6

Table 6 - Number of Subjects Completing Treatment and/or Follow-up (Study 049)

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects Completing Treatment	35 (70%)	48 (96%)
Subjects who Completed Study	34	45
Subjects who Discontinued Study	1	3
Subjects Discontinuing Treatment	15 (30%)	2 (4%)
Subjects who Completed Study	12	1
Subjects who Discontinued Study	3	1

Table 7 – Reasons for Early Treatment Discontinuation (Study 048)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
Number of Subjects	353	349	70	69
Subjects who Disc Trt	47	79	2	6
Adverse Event	35 (local AE [35])	49 (local AE [48])	2	-
Lost to Follow-Up	-	3	-	1
Noncompliance	-	1	-	-
Subject's Decision	11 (local AE [3])	18 (local AE [6])	-	5
Other	1 (local AE)	8 (local AE [5])	-	-

Table 8 - Reasons for Early Treatment Discontinuation (Study 049)

	4% 5-FU	Vehicle
Number of Subjects	50	50
Subjects who Discontinued Trt	15	2
Adverse Event	11 (local AE [11])	2
Lost to Follow-Up	1	-
Noncompliance	1	-
Subject's Decision	1	-
Other	1	-

The sponsor noted that three subjects in Study 048 (4-263 [Vehicle QD], 12-98 [4% 5-FU], and 15-765 [Efudex]) 'forgot to start their medication so the subjects were re-randomized at Visit 2 (which became a replacement Baseline visit and Visit 2 was re-scheduled).' (p. 54 of the study report) Subject 4-263 started treatment 14 days after signing the informed consent, Subject 12-98 started treatment 15 days after signing the informed consent, and Subject 15-765 started treatment 3 days after signing the informed consent. In a clarifying communication from the sponsor (dated 3/25/2008), the sponsor clarified that the subjects were not 're-randomized', but were re-evaluated by study staff to ensure there were no changes to baseline information when it was discovered the subjects had not started medication. In each case the baseline date was changed by the investigator to the re-evaluation date. Although this appears to be highly unusual, this issue involves 3 subjects, each on different treatment arms and at different centers, in a study with over 800 subjects and does not appear to impact the conclusions of the study.

3.1.3 Baseline Characteristics

The demographics were generally well-balanced across the treatment arms in Study 048. In Study 049, which enrolled only 100 subjects, had some imbalances with regard to gender and baseline lesion counts. The mean age of subjects was around 67 years and about 80% of the subjects were male in both studies. In Study 049, of the 15 female subjects, 11 were randomized to 5-FU while only 4 were randomized to vehicle. About

4% of the subjects in Study 048 were Latino, although none of the subjects in Study 049 were. Nearly all of the subjects were white. The average number of baseline lesions in Study 048 was 14.7 and was fairly balanced across treatment arms. The average number of baseline lesions in Study 049 was higher at 21.2, with 19.2 for 4% 5-FU and 23.2 for vehicle. Baseline characteristics are presented in Table 9 and Table 10.

Table 9 – Baseline Characteristics (Study 048)

	4% 5-FU N=353	Efudex N=349	Vehicle QD N=70	Vehicle BID N=69
Age (years)				
Mean	67.7	67.4	68.0	69.1
Range	36 - 88	37 - 94	47 - 84	37 - 88
Gender				
Male	287 (81%)	282 (81%)	58 (83%)	55 (80%)
Female	66 (19%)	67 (19%)	12 (17%)	14 (20%)
Ethnicity				
Hispanic/Latino	15 (4%)	17 (5%)	1 (1%)	3 (4%)
Not Hisp/Latino	338 (96%)	332 (95%)	69 (99%)	66 (96%)
Race				
White	348 (99%)	347 (99%)	70 (100%)	69 (100%)
Am. Ind./AK Native	1 (<1%)	-	-	-
Other	4 (1%)	2 (1%)	-	-
Lesions				
Mean	14.4	14.8	16.2	14.7
Range	5 - 82	5 - 76	5 - 90	5 - 49

Table 10 – Baseline Characteristics (Study 049)

	4% 5-FU N=50	Vehicle N=50
Age (years)		
Mean	67.9	66.9
Range	44-85	33-87
Gender		
Male	39 (78%)	46 (92%)
Female	11 (22%)	4 (8%)
Ethnicity		
Not Hisp/Latino	50 (100%)	50 (100%)
Race		
White	50 (100%)	50 (100%)
Lesions		
Mean	19.2	23.2
Range	5 - 83	6 - 80

3.1.4 Efficacy Results

Tradename (4% 5-FU) was superior to its vehicle for the primary endpoint (100% clearance 4 weeks post-treatment) in both Studies 048 ($p < 0.001$) and 049 ($p = 0.004$). Study 048 failed to demonstrate that 4% 5-FU was non-inferior to Efudex for the primary endpoint (97.5% lower confidence bounds of -11.1% (ITT) and -12.8% (PP) with a non-inferiority margin of 10%). The test product (4% 5-FU) was also superior to its vehicle for the two secondary endpoints of the proportion with at least 75% clearance and the percent reduction in lesions at 4 weeks post-treatment. Efficacy results for the ITT population are presented in Table 11 and Table 12. The results for the per protocol population are similar and are presented in Table 13 and Table 14. Of note, the clearance rate for 4% 5-FU was higher in Study 048 than 049 (54% vs. 24%). The reason for this difference is not clear, but this issue is explored in Section 3.1.8 below. Estimates for the mean number of lesions and percent reduction in lesions at the end of the study are particularly sensitive to the handling of missing data. The differences between the ITT and per protocol analyses for the final lesion counts (7.1 (ITT) vs. 4.2 (PP)) and percent change in lesions (57% (ITT) vs. 74% (PP)) in Study 049 for 4% 5-FU is due to a small number of subjects who did not attend the final study visit and carried forward large lesion counts for the analysis. (See Section 3.1.7 for further discussion.) In particular, most of this difference is due to the one subject in Study 049 who died with 123 lesions carried forward. If this subject is excluded from the ITT analysis of Study 049, the mean number of lesions at the end of the study for 4% 5-FU drops from 7.1 to 4.7 while the mean percent reduction increases from 57% to 70%.

Table 11 – Efficacy Results for Study 048 (ITT-LOCF)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID	p-value / LCB
	N=353	N=349	N=70	N=69	
Baseline Count (Mean)	14.4	14.8	16.2	14.7	
End of Study Count (Mean)	2.4	2.6	13.9	11.6	
Percent Reduction (Mean)	81.2%	80.0%	17.7%	20.2%	<0.001[a] -5.0%[b]
75% Clearance	284 (80%)	280 (80%)	5 (7%)	7 (10%)	<0.001[c] -5.9%[d]
Primary Endpoint: 100% Clearance	192 (54%)	202 (58%)	3 (4%)	3 (4%)	<0.001[c] -11.1%[d]

[a] Treatment p-value for 4% 5-FU vs. vehicle based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and vehicle groups
[b] 97.5% lower confidence bound for 4% 5-FU vs. Efudex based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and Efudex groups
[c] P-value for 4% 5-FU vs. vehicle based on a CMH test stratified by grouped investigator
[d] 97.5% lower confidence bound for 4% 5-FU vs. Efudex based on Wald's confidence interval with Yate's continuity correction

Table 12 – Efficacy Results for Study 049 (ITT-LOCF)

	4% 5-FU	Vehicle	p-value
	N=50	N=50	
Baseline Count (Mean)	19.2	23.2	
End of Study Count (Mean)	7.1	21.7	
Percent Reduction (Mean)	56.9%	4.3%	<0.001
75% Clearance	37 (74%)	5 (10%)	<0.001
Primary Endpoint: 100% Clearance	12 (24%)	2 (4%)	0.004

Table 13 – Efficacy Results for Study 048 (PP)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID	p-value / LCB
	N=326	N=307	N=63	N=61	
Baseline Count (Mean)	14.4	15.0	16.6	15.0	
End of Study Count (Mean)	2.1	1.8	14.2	11.5	
Percent Reduction (Mean)	84.3%	87.7%	17.7%	22.9%	<0.001 -7.9%
75% Clearance	269 (83%)	261 (85%)	5 (8%)	7 (11%)	<0.001 -8.6%
Primary Endpoint: 100% Clearance	182 (56%)	186 (61%)	3 (5%)	3 (5%)	<0.001 -12.8%

[a] Treatment p-value for 4% 5-FU vs. vehicle based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and vehicle groups
[b] 97.5% lower confidence bound for 4% 5-FU vs. Efudex based on an ANOVA with factors for treatment and grouped investigator, limited to 4% 5-FU and Efudex groups
[c] P-value for 4% 5-FU vs. vehicle based on a CMH test stratified by grouped investigator
[d] 97.% lower confidence bound for 4% 5-FU vs. Efudex based on Wald's confidence interval with Yate's continuity correction

Table 14 – Efficacy Results for Study 049 (PP)

	4% 5-FU	Vehicle	p-value
	N=43	N=44	
Baseline Count (Mean)	19.9	23.5	
End of Study Count (Mean)	4.2	21.7	
Percent Reduction (Mean)	74.3%	6.6%	<0.001
75% Clearance	36 (84%)	5 (11%)	<0.001
Primary Endpoint: 100% Clearance	12 (28%)	2 (5%)	0.004

3.1.5 Lesion Counts over Time

Subjects treated with 5-FU in the studies typically experienced an increase in lesions during treatment before experiencing improvement by the follow-up visits. At some visits, especially at Week 4, the investigators were unable to count lesions on some subjects, with investigators stating that the lesions were too numerous to count or stating that that the count could not be done due to inflammation or erythema. In particular, 92/353 (26%) of 4% 5-FU subjects in Study 048 attended the Week 4 visit but were marked as having lesion counts 'Not Done'. In Study 049 the proportion of 4% 5-FU subjects with counts 'Not Done' at Week 4 was 25/50 (50%). As these subjects did not have a numeric count recorded, means and medians for lesion counts are not interpretable at visits with high proportions of subjects with uncountable lesions. Figure 1 and Figure 2 display boxplots of the observed lesion counts by visit along with pie charts of the proportion of subjects contributing numerical data to the boxplots for subjects treated with 4% 5-FU. Although the number of lesions at Visit 4 appears to peak at Visit 4 (Week 4) in Study 048 and at Visit 3 (Week 2) in Study 049, only about 1/3 of subjects were able to have lesion counts done at that Visit 4 in Study 049. A full 50% of the subjects were not evaluable and an additional 18% of subjects did not attend Visit 4. Subjects treated with vehicle tended to have stable counts similar to baseline throughout the study (data not shown).

Figure 1 – Observed Lesion Counts by Visit and the Proportion of Subjects without Observed Counts for 4% 5-FU (Study 048)

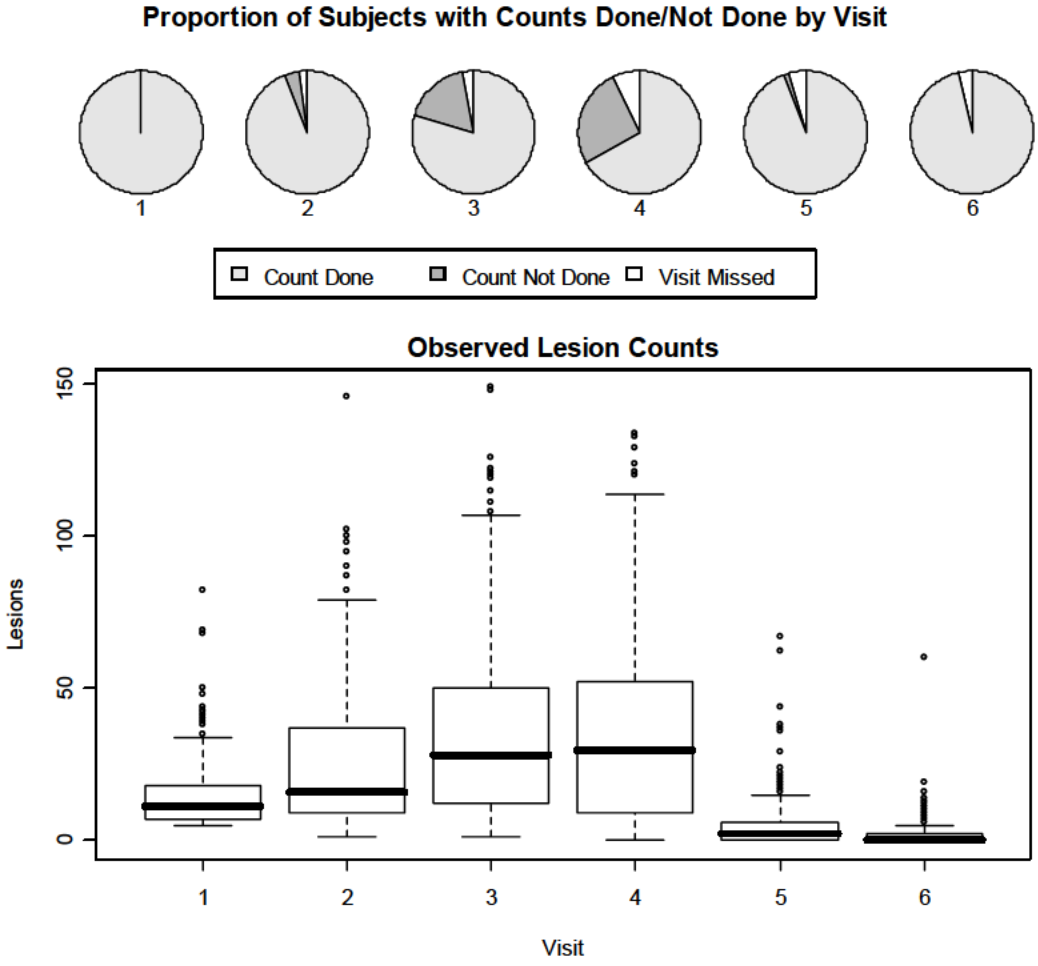
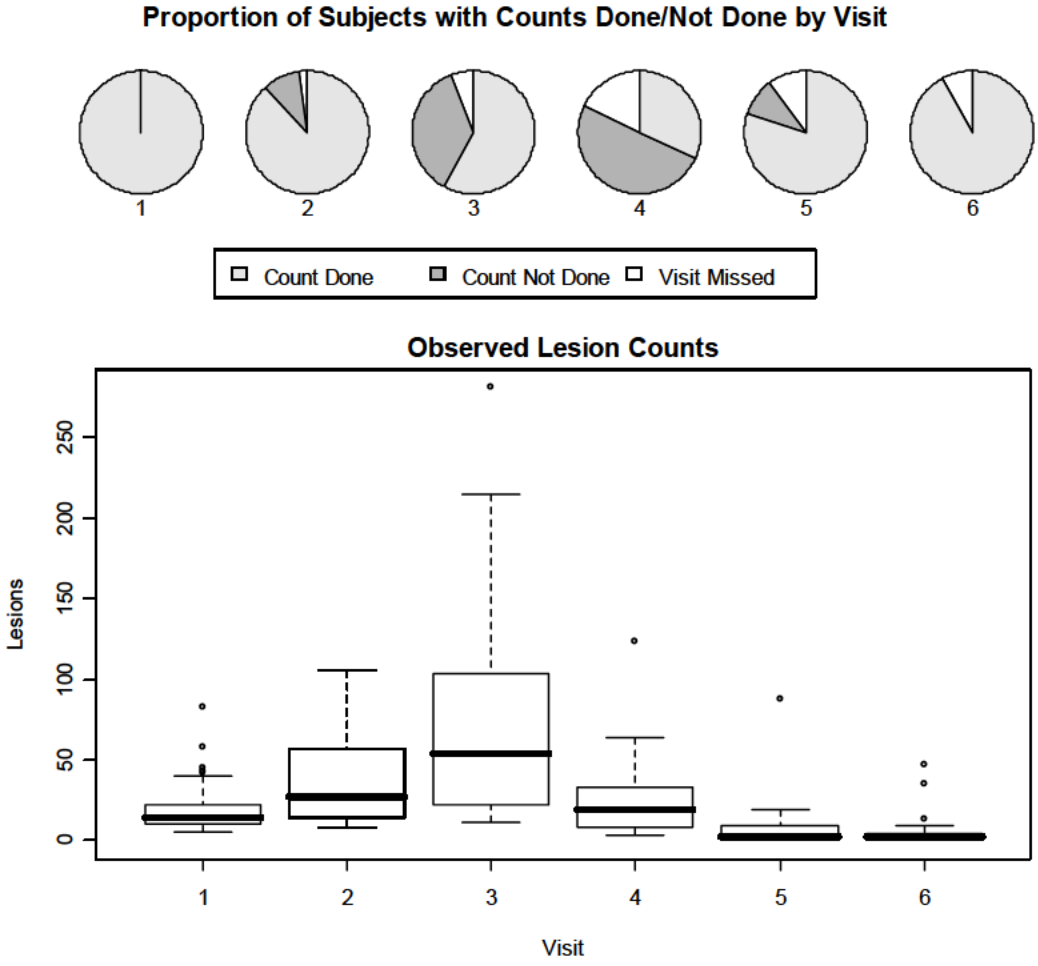


Figure 2 - Observed Lesion Counts by Visit and the Proportion of Subjects without Observed Counts for 4% 5-FU (Study 049)



3.1.6 Efficacy Results by Center

Clearance rates varied from center to center, but the clearance rate was higher on the active treatment arms than vehicle at all centers of at least moderate size. Clearance rates by center are presented in Figure 3 and Figure 4.

Figure 3 – 100% Clearance Rates by Center

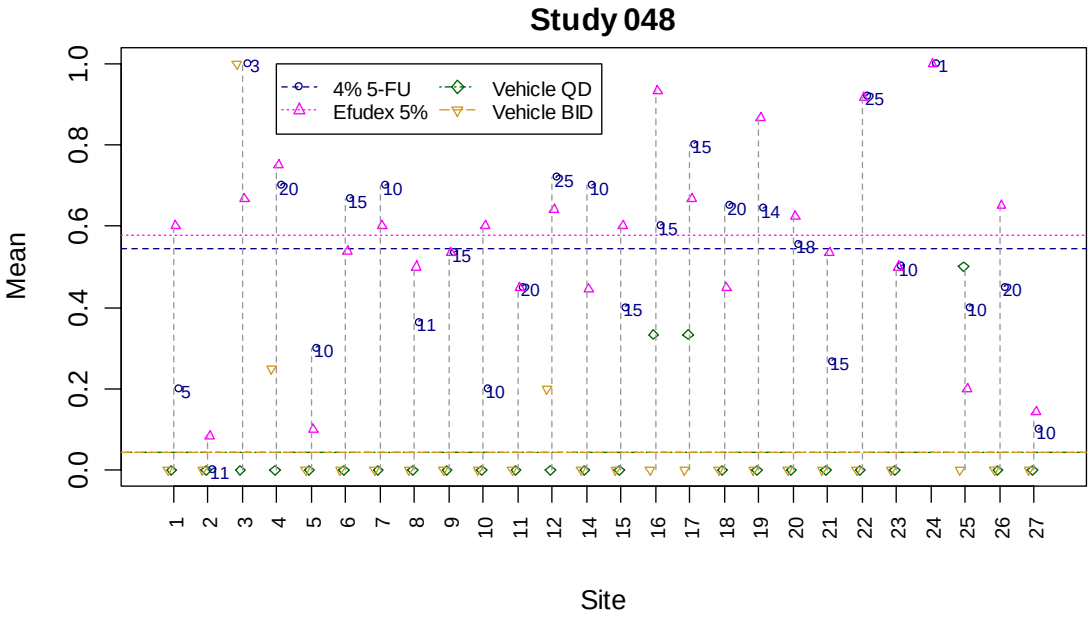
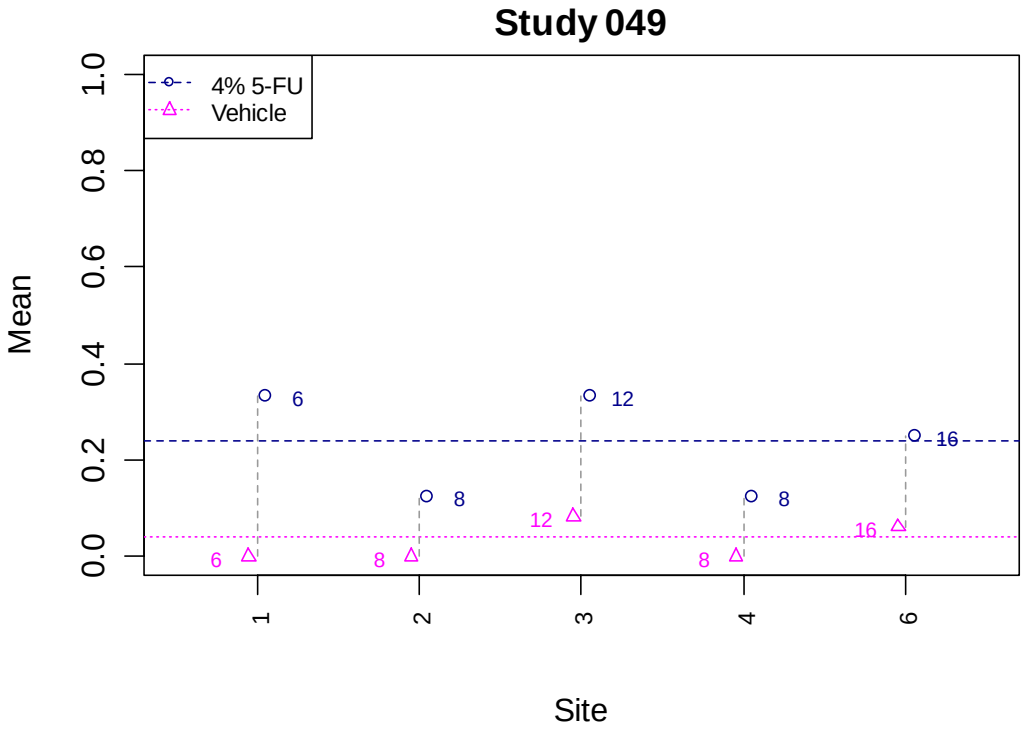


Figure 4 – 100% Clearance Rates by Center

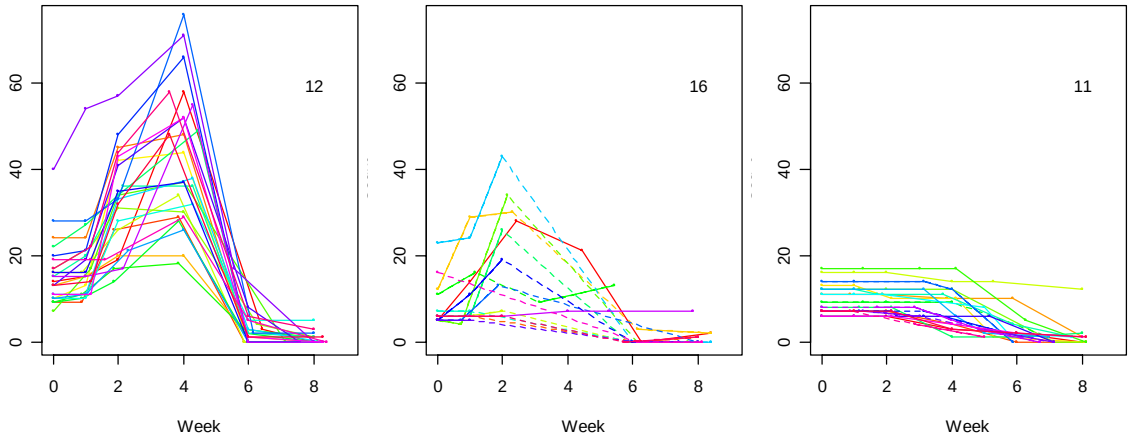


As noted in the previous section, most subjects receiving active treatment experience an increase in lesions during treatment. Some investigators were able to count lesions on all returning subjects at all visits, while other investigators were unable to record lesion counts for subjects at some visits, particularly Week 4, due to either inflammation or

lesions being too numerous. However, a few investigators had subjects with flat profiles, that is, the 5-FU subjects did not experience an increase in lesions during the study. Figure 5 presents the lesion count profiles for 4% 5-FU subjects for three selected investigators. The selected investigators represent the typical patterns observed in Study 048. The first panel (Investigator 12) presents data from an investigator that collected lesion counts at every visit for most subjects. The second panel (Investigator 16) presents data from an investigator who marked 'Not Done' for many subjects at the Week 2 or Week 4 visits. Dashed lines in this plot represent a subject with a missing count between two observed counts. These two investigators are fairly representative of the profiles observed on 5-FU subjects for most of the investigators. However, in the third panel (Investigator 11), the profiles from this investigator are notable in that none of the subjects had an increase in lesions recorded during the treatment period.

It is not clear whether the subjects truly did not experience any increase in lesions or whether the investigator only tracked and counted lesions present at baseline. A DSI inspection report for Investigator 11 is pending at the time of this review. Three investigators (2, 3, and 11) in Study 048 enrolling 34 4% 5-FU subjects reported a flat, non-increasing lesion count profile in nearly all of their subjects. As can be seen in Figure 3, Investigators 2 and 11 had smaller than average treatment effects for 4% 5-FU versus vehicle (Investigator 3 enrolled very few subjects), so these centers are not driving the efficacy results or biasing results in favor of 4% 5-FU, whatever the reason for the difference in profiles.

Figure 5 - Lesion Count Profiles for 4% 5-FU Subjects for Selected Investigators (Study 048)



3.1.7 Impact of Dropouts on Efficacy Analysis

As noted in the previous sections, subjects who received 5-FU treatment usually experienced an increase in lesions during treatment. Therefore, subjects on the active treatment arms who dropped out of the study early frequently had larger lesion counts carried forward to the final analysis. Subjects receiving vehicle typically remained close to their baseline lesion count throughout the study. Thus the LOCF analysis appears to be a reasonable approach to handling missing data in this case. Subjects who drop out of

the active arms tend to carry forward a worse result than subjects who are followed to the end of the trial, while subjects who drop out of the vehicle arms tend to carry forward a similar result to the subjects who are followed to the end of the trial. Figure 6 and Figure 7 present the final observed lesion counts by baseline lesion counts for subjects who attended the final visit and for subjects who discontinued early.

Figure 6 – Baseline by Final Lesion Counts (Study 048)

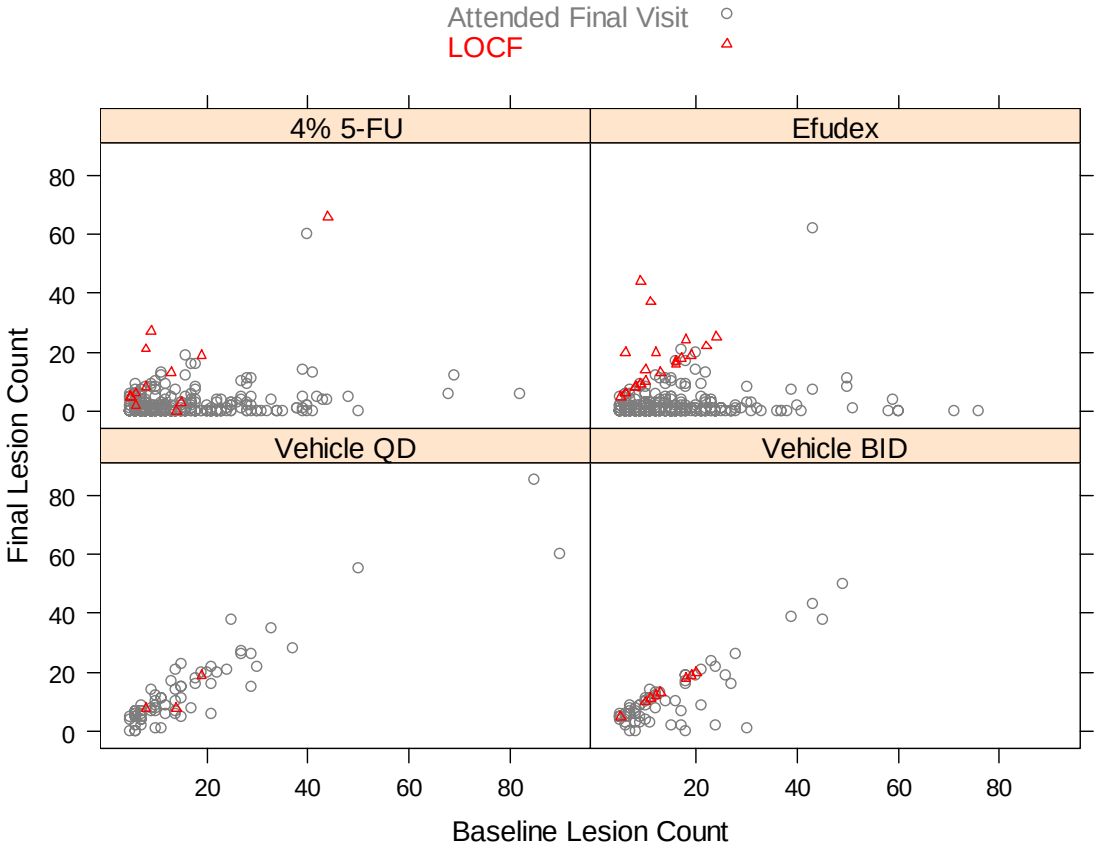
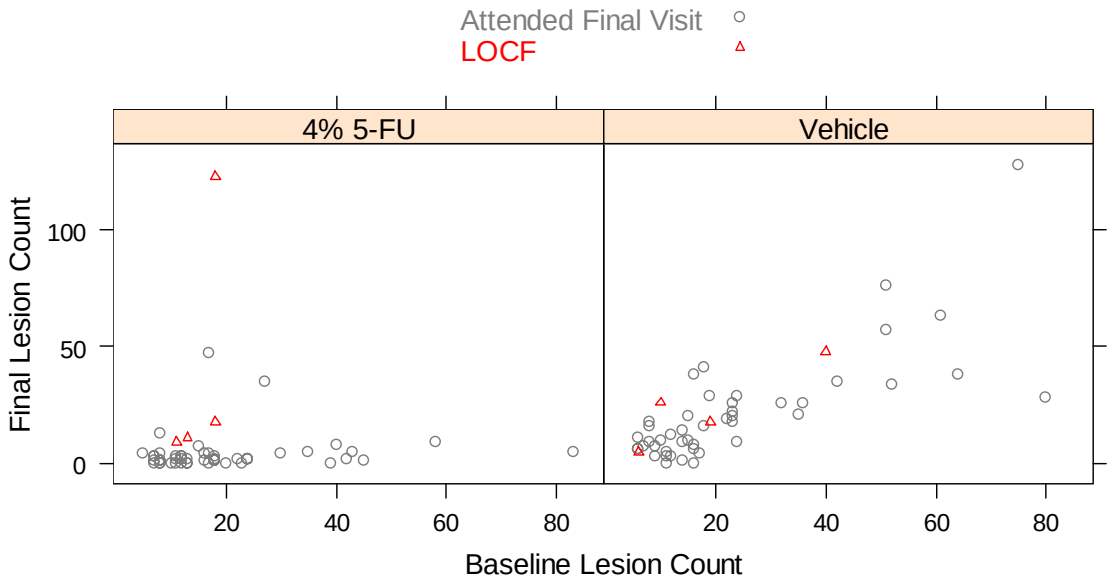


Figure 7 – Baseline by Final Lesion Counts (Study 049)



Some subjects did not complete the full treatment regimen. To assess the impact of the length of treatment on the final clearance assessment, this reviewer grouped the subjects by the number of days treated. The expected number of treatment days was 28. The groupings were selected to roughly correspond to one week intervals. In Study 048, subjects who had at least 12 days of treatment had similar success rates to those who completed the study, while subjects with less than 12 days of treatment had lower success rates. In Study 049, the number of subjects who did not complete treatment is too small to make any meaningful comparisons.

Table 15 – 100% Clearance Rates by Number of Days Treated (Study 048)

	4% 5-FU	Efudex	Vehicle QD	Vehicle BID
< 12 Days	2/10 (20%)	1/11 (9%)	0/1 (0%)	0/2 (0%)
12 – 20 Days	10/20 (50%)	28/41 (68%)	-	-
21 – 25 Days	14/28 (50%)	18/29 (62%)	0/1 (0%)	-
> 25 Days	166/288 (58%)	154/256 (60%)	3/68 (4%)	3/63 (5%)
Missing Days	0/7 (0%)	1/12 (8%)	-	0/4 (0%)

Table 16 - 100% Clearance Rates by Number of Days Treated (Study 049)

	4% 5-FU	Vehicle
< 12 Days	1/5 (20%)	0/1 (0%)
12 – 20 Days	0/5 (0%)	0/1 (0%)
21 – 25 Days	1/3 (33%)	0/1 (0%)
> 25 Days	10/35 (29%)	2/47 (4%)
Missing Days	0/2 (0%)	-

3.1.8 Difference in Clearance Rates between Study 048 and Study 049

Study 049 has a noticeably smaller clearance rate for 4% 5-FU than Study 048, even though the vehicle rates are comparable. Potential reasons for this could include the fact that the sample size in Study 049 was many times smaller than the sample size in Study 048 (and thus the point estimate in Study 049 is less precise), differences in subject populations, or issues related to the conduct of the studies. To assess the impact of the sample size on the precision of the point estimates, this reviewer calculated the 95% confidence intervals for the 4% 5-FU clearance rates in the two studies. In Study 048, the confidence interval for the estimated clearance rate of 192/353 (54%) is (49%, 59%). In Study 049, the confidence interval for the estimated clearance rate of 12/50 (24%) is (12%, 36%). Since these confidence intervals do not overlap, the lower level of precision associated with the estimate from the second study is unlikely to be the only reason that that study has a much smaller clearance rate estimate than the first study.

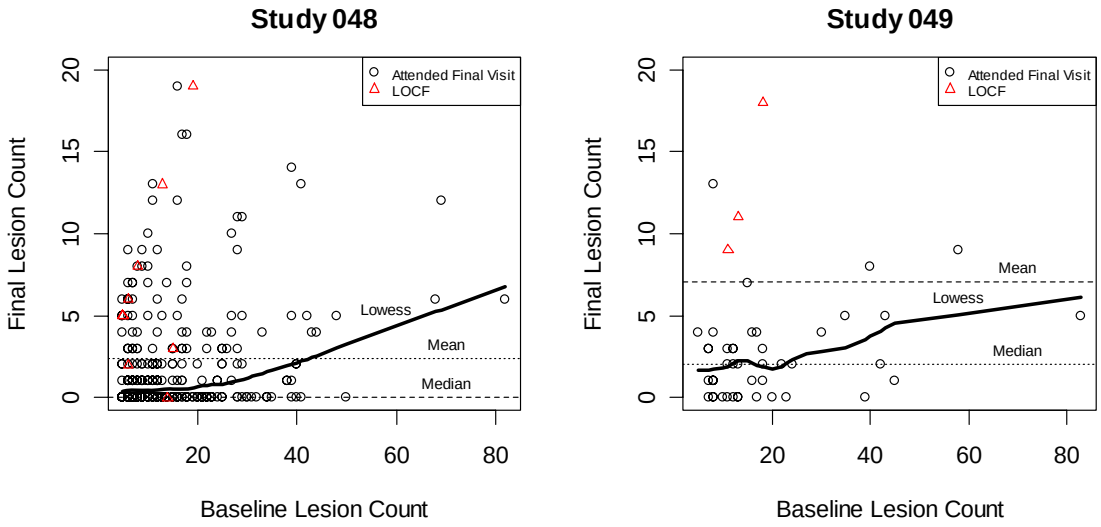
Another possibility is that the subject populations between the two studies differed. One baseline difference between the study populations was the baseline lesion counts. For 4% 5-FU, the baseline lesion count in Study 048 was 14.4 and in Study 049 it was 19.2. The protocol defined 3 categories of baseline severity for subgroup analysis: mild = 5 – 10 lesions, moderate = 11-25 lesions, and severe = more than 25 lesions. The analysis by baseline lesion groupings is presented in Section 4.2. In each study, the 4% 5-FU clearance rates were similar for subjects with 5-10 or 11-25 lesions at baseline, while the clearance rate for subjects with more than 25 lesions was lower. In Study 048, the clearance rates by grouping for 4% 5-FU were for 5-10 lesions: 58% (99/171), for 11-25 lesions: 57% (79/138), and for >25 lesions: 32% (14/44). In Study 049, the clearance rates by grouping for 4% 5-FU were for 5-10 lesions: 31% (4/13), for 11-25 lesions: 26% (7/27), and for >25 lesions: 10% (1/10).

To further explore the impact of baseline lesion counts, Figure 8 presents scatterplots of baseline counts versus final lesion counts for 4% 5-FU. The scatterplots include lines for the overall mean and median final lesion counts along with lowess smoothing. The lowess line tracks a ‘likely’ estimate for the final lesion count based on the information from subjects with similar baseline counts, and is not restricted to any particular form, such as a straight line. Both studies have a similarly shaped ‘hockey stick’ smoothing pattern. In each study, subjects enrolled with 20 or fewer lesions demonstrate a flat response, that is, subjects are likely to achieve a comparable final lesion count regardless of the baseline. For subjects enrolled with more than 20 lesions, the final lesion count appears to be approximately linearly related to the baseline count. The difference between the two studies is that subjects in Study 049 reduced to a median of about 3 lesions, while subjects in Study 048 reduced to a median of 0. Thus the lowess line and the analysis of the clearance rate by baseline grouping have similar interpretations, namely that the baseline lesion count impacts the final number of lesions only when the baseline count is greater than about 20 to 25 lesions.

These two analyses also demonstrate that the differing efficacy rates for 4% 5-FU in Studies 048 and 049 can also not be completely explained by differences in baseline lesion counts, as the clearance rates for Study 048 are still higher than 049 even when the

baseline count has been taken into account. Thus, the differing response rates between the two studies may be due some other unidentified difference in the study subjects or other unidentified differences in how the studies were conducted.

Figure 8 – Baseline by Final Lesion Counts with Smoothing for 4% 5-FU



Note: Y-axis range has been truncated to show detail at the lower end of the range. See the comparable plots in Figure 6 and Figure 7 to see the full range, including outliers.

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

Among subjects with dosing information available in Study 048, 4% 5-FU subjects applied treatment for a mean of 26.5 dosing days (range 2 to 35, N=346), Efudex subjects applied treatment for a mean of 25.8 dosing days (range 1 to 41, N=337), vehicle QD subjects applied treatment for a mean of 28.1 dosing days (range 11 to 33, N=70), and vehicle BID subjects applied treatment for a mean of 28.0 dosing days range (6 to 33, N=65). Among subjects with dosing information available in Study 049, 4% 5-FU subjects applied treatment for a mean of 24.9 dosing days (range 7 to 44, N=48), and vehicle subjects applied treatment for a mean of 28.0 dosing days (range 6 to 36, N=50).

3.2.2 Local Tolerance Assessments

Seven assessments of local tolerance (erythema, scaling/dryness, crusting, pruritus, stinging/burning, edema, and erosions) were assessed at every visit on a 4-point scale (0 – none, 1 – mild, 2 – moderate, 3 – severe). Each of these assessments increased in mean severity throughout the treatment period on the 5-FU arms, peaking at Week 4 (Visit 4). During the post-treatment period the mean severity returned to baseline levels. Subjects on vehicle treatment remained on average at baseline levels throughout the study. The mean values for the 4% 5-FU arm were slightly lower than the Efudex mean values. Local tolerance assessments were conducted on the safety population, defined as all randomized subjects with documented use of at least one application of study medication

and at least one post-baseline assessment. The mean values for the local tolerance assessments at each visit are presented in Figure 9 and Figure 10.

Figure 9 – Mean Local Tolerance Scores by Visit (Observed Data – Study 048)

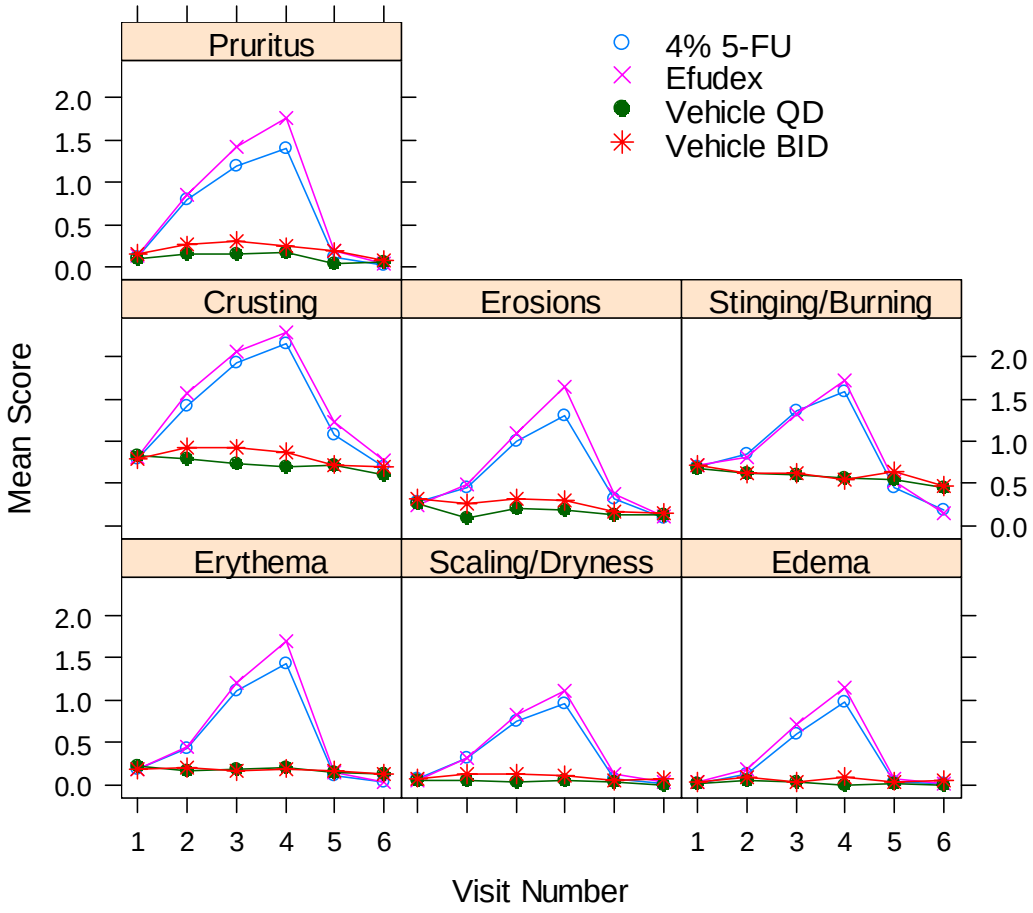
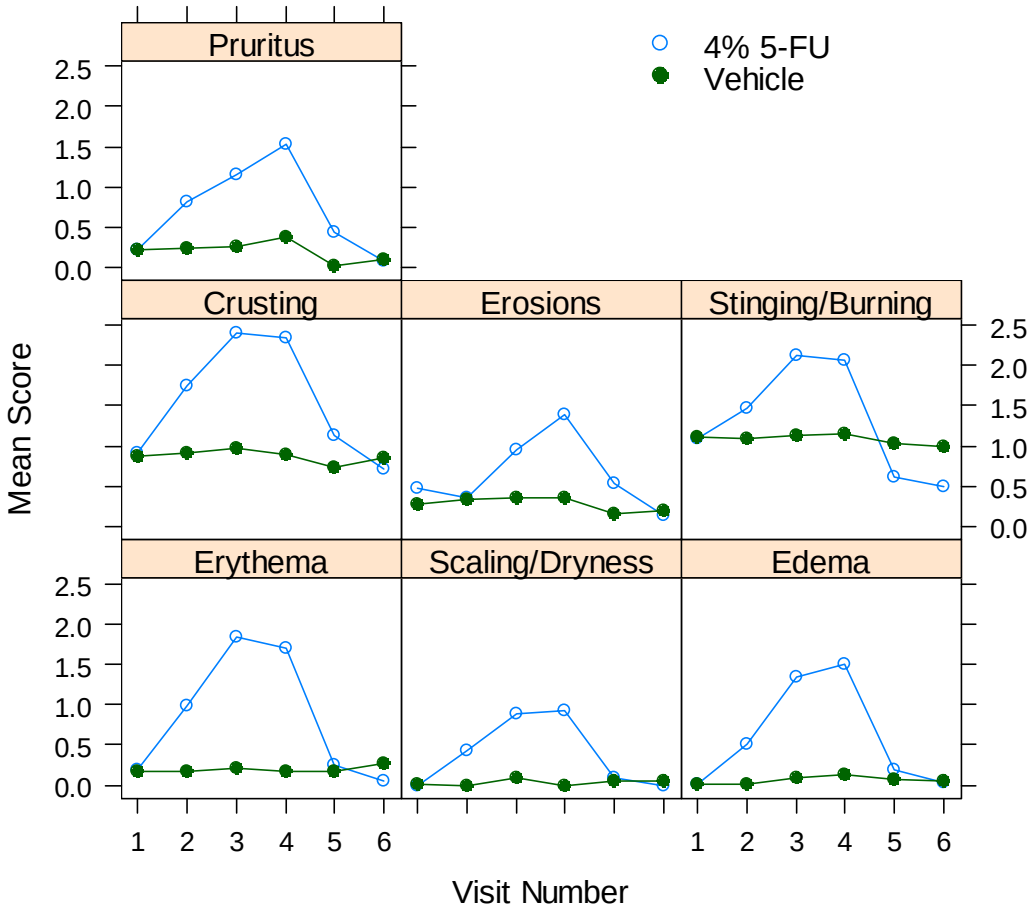


Figure 10 - Mean Local Tolerance Scores by Visit (Observed Data – Study 049)



Although most 5-FU subjects experienced their maximum severity for the local tolerance assessments at Week 4, some subjects experienced their maximum at earlier visits or were not present at the Week 4 visit. The vast majority of 5-FU subjects experienced local tolerance events, and many of them had severe events. The number of subjects who experienced any level of an assessment (mild, moderate, or severe) during the study along with the number of subjects experiencing severe events are presented in Table 17 and Table 18.

Table 17 – Maximum Local Tolerance Assessment (Safety Population – Study 048)

	4% 5-FU N=348		Vehicle QD N=70	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	345 (99%)	142 (41%)	55 (79%)	0 (0%)
Scaling/Dryness	328 (94%)	71 (20%)	49 (70%)	0 (0%)
Crusting	298 (86%)	69 (20%)	21 (30%)	0 (0%)
Pruritus	297 (85%)	58 (17%)	27 (39%)	0 (0%)
Stinging/Burning	300 (86%)	89 (26%)	22 (31%)	0 (0%)
Edema	234 (67%)	27 (8%)	5 (7%)	0 (0%)
Erosions	231 (66%)	34 (10%)	4 (6%)	0 (0%)
	Efudex N=342		**Vehicle BID N=65**	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	337 (99%)	169 (49%)	58 (89%)	2 (3%)
Scaling/Dryness	325 (95%)	84 (25%)	44 (68%)	1 (2%)
Crusting	315 (92%)	89 (26%)	19 (29%)	0 (0%)
Pruritus	305 (89%)	84 (25%)	30 (46%)	0 (0%)
Stinging/Burning	315 (92%)	116 (34%)	26 (40%)	0 (0%)
Edema	250 (73%)	34 (10%)	9 (14%)	0 (0%)
Erosions	259 (76%)	46 (13%)	10 (15%)	0 (0%)

*Mild, moderate, or severe

Table 18 - Maximum Local Tolerance Assessment (Safety Population – Study 049)

	4% 5-FU N=49		Vehicle N=50	
	All Grades*	**Severe**	**All Grades***	**Severe**
Erythema	49 (100%)	32 (65%)	47 (94%)	0 (0%)
Scaling/Dryness	49 (100%)	23 (47%)	50 (100%)	0 (0%)
Crusting	48 (98%)	18 (37%)	25 (50%)	0 (0%)
Pruritus	40 (82%)	7 (14%)	19 (38%)	1 (2%)
Stinging/Burning	46 (94%)	12 (24%)	20 (40%)	0 (0%)
Edema	41 (84%)	3 (6%)	6 (12%)	0 (0%)
Erosions	40 (82%)	10 (20%)	10 (20%)	0 (0%)

*Mild, moderate, or severe

3.2.3 Adverse Events

Many of the adverse events in the study were captured via the local tolerance assessments. In addition to the events reported under the active surveillance, 5-FU subjects also reported application site reaction, irritation, inflammation and pain. Events occurring in >1% of subjects treated with 5-FU are presented in Table 19 and Table 20.

Table 19 – Adverse Events in >1% of 5-FU Subjects (Safety Population – Study 048)

	4% 5-FU N=348	Efudex N=342	Vehicle QD N=70	Vehicle BID N=65
Subjects Reporting Events	118 (34%)	122 (36%)	16 (23%)	13 (20%)
Application site irritation	25 (7%)	27 (8%)	0 (0%)	0 (0%)
Application site reaction	12 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site erythema	10 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site pruritus	10 (3%)	15 (4%)	0 (0%)	0 (0%)
Application site pain	9 (3%)	16 (5%)	0 (0%)	0 (0%)
Application site edema	8 (2%)	2 (<1%)	0 (0%)	0 (0%)
Application site inflammation	3 (1%)	4 (1%)	0 (0%)	0 (0%)
Impetigo	2 (<1%)	7 (2%)	0 (0%)	0 (0%)
Nasopharyngitis	1 (<1%)	4 (1%)	1 (1%)	0 (0%)
Application site infection	0 (0%)	4 (1%)	0 (0%)	0 (0%)
Headache	1 (<1%)	6 (2%)	1 (1%)	0 (0%)
Diarrhea	5 (1%)	1 (<1%)	0 (0%)	1 (2%)
Nausea	4 (1%)	1 (<1%)	0 (0%)	1 (2%)
Vomiting	4 (1%)	0 (0%)	0 (0%)	0 (0%)
Eye irritation	4 (1%)	1 (<1%)	0 (0%)	0 (0%)
Back pain	4 (1%)	0 (0%)	1 (1%)	0 (0%)

Table 20– Adverse Events in >1% of 5-FU Subjects (Safety Population – Study 049)

	4% 5-FU N=49	Vehicle N=50
Subjects Reporting Events	21 (43%)	6 (12%)
Application site pain	7 (14%)	0 (0%)
Application site reaction	4 (8%)	1 (2%)
Application site irritation	4 (8%)	0 (0%)
Application site erythema	2 (4%)	0 (0%)
Application site inflammation	2 (4%)	0 (0%)
Application site edema	2 (4%)	0 (0%)
Application site dermatitis	1 (2%)	1 (2%)
Application site pruritus	1 (2%)	0 (0%)
Application site dryness	1 (2%)	0 (0%)
Application site erosion	1 (2%)	0 (0%)
Application site paraesthesia	1 (2%)	0 (0%)
Nasopharyngitis	1 (2%)	0 (0%)
Pharyngitis	1 (2%)	0 (0%)
Dementia Alzheimer’s type	1 (2%)	0 (0%)
Headache	1 (2%)	0 (0%)
Angina pectoris	1 (2%)	0 (0%)
Myocardial infarction	1 (2%)	0 (0%)
Eye swelling	1 (2%)	0 (0%)
Joint swelling	1 (2%)	0 (0%)
Vein Discoloration	1 (2%)	0 (0%)

One subject died during the study. The subject was treated with 4% 5-FU and had a heart attack and died one day after completing the 4-week treatment period. The subject was an 82 year old male and had a history of hypertension, hypercholesterolemia, and a quadruple bypass. The investigator classified the death as unrelated to study medication. The key efficacy and safety data for this subject are presented in Table 21.

Table 21 – Subject 049-73 Data

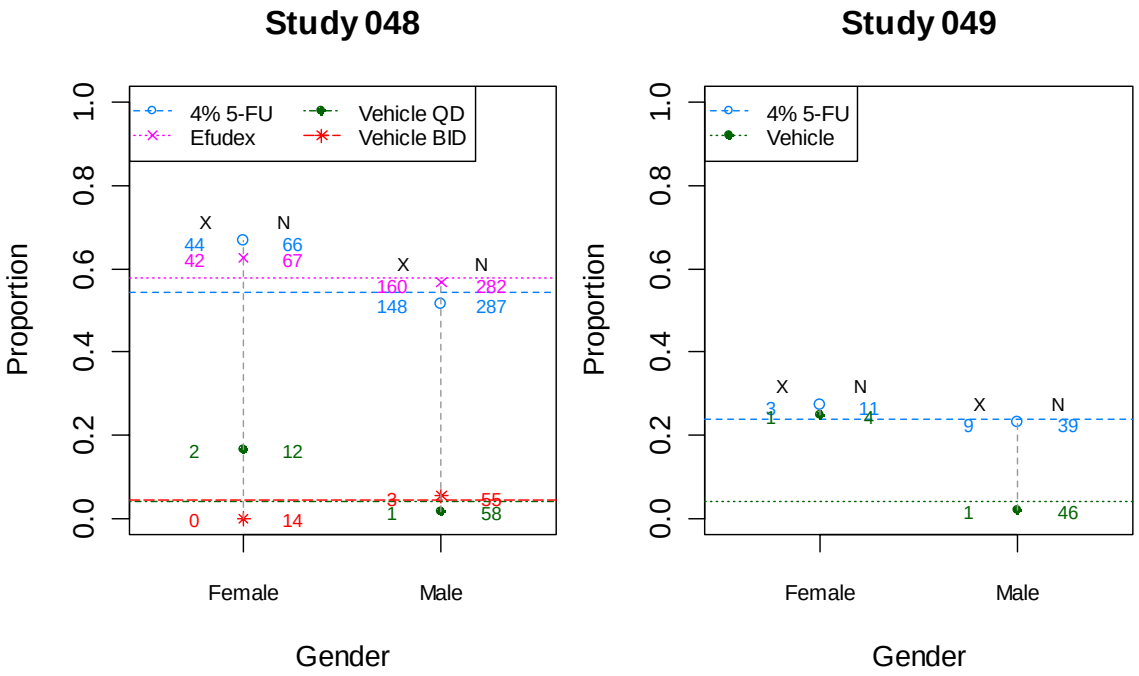
Visit	1	2	3	4	5	6
Visit Date	10AUG06	16AUG06	28AUG06	07SEP06	-	-
Days from Baseline	0	6	18	28	-	-
Lesions	18	51	87	123	-	-
Crusting	1	2	2	3	-	-
Edema	0	0	1	1	-	-
Erosions	0	0	1	2	-	-
Erythema	0	1	2	3	-	-
Pruritus	0	0	1	1	-	-
Scaling	1	2	2	2	-	-
Stinging	0	0	0	1	-	-
Adverse Event: Myocardial Infarction (08SEP06) resulting in death.						

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

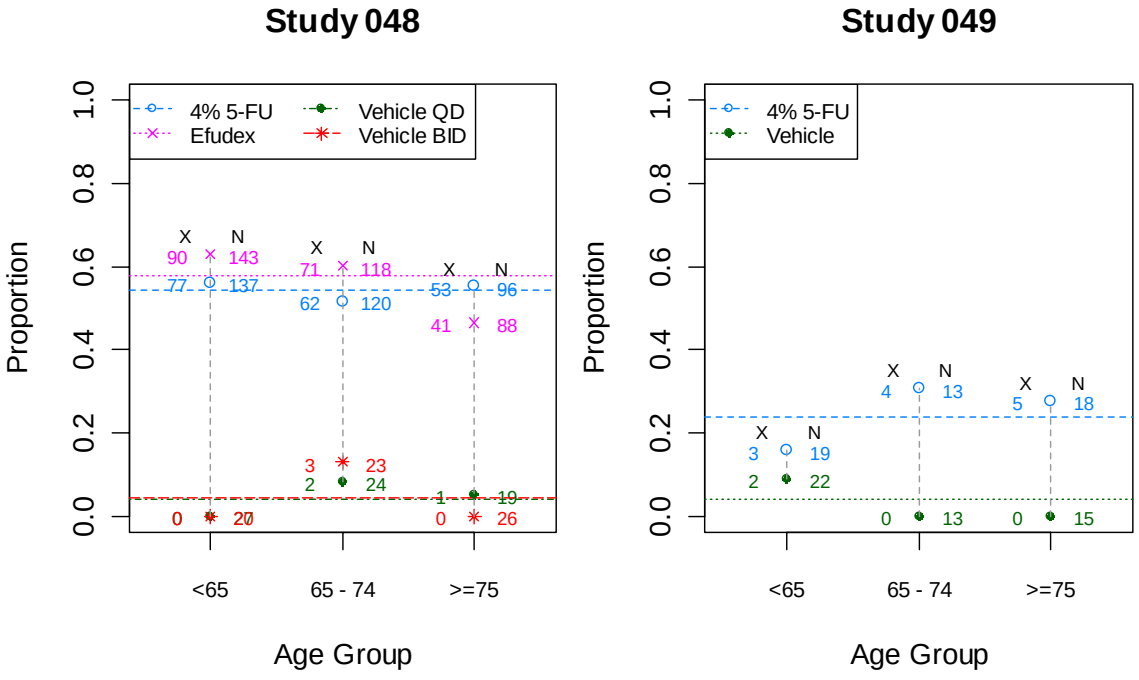
The studies were not powered to detect differences in subgroups, however, no obvious efficacy differences were noted in gender or age subgroups. Nearly all the enrolled subjects (>99%) were white so analyses by race are not informative. Study 049 only enrolled 15 female subjects and 11 of these subjects were randomized to 4% 5-FU. Clearance rates by gender and age are presented in Figure 11 and Figure 12.

Figure 11 – Clearance rates by Gender



Note: X = Number cleared, N = Subgroup size

Figure 12 – Clearance Rates by Age Group

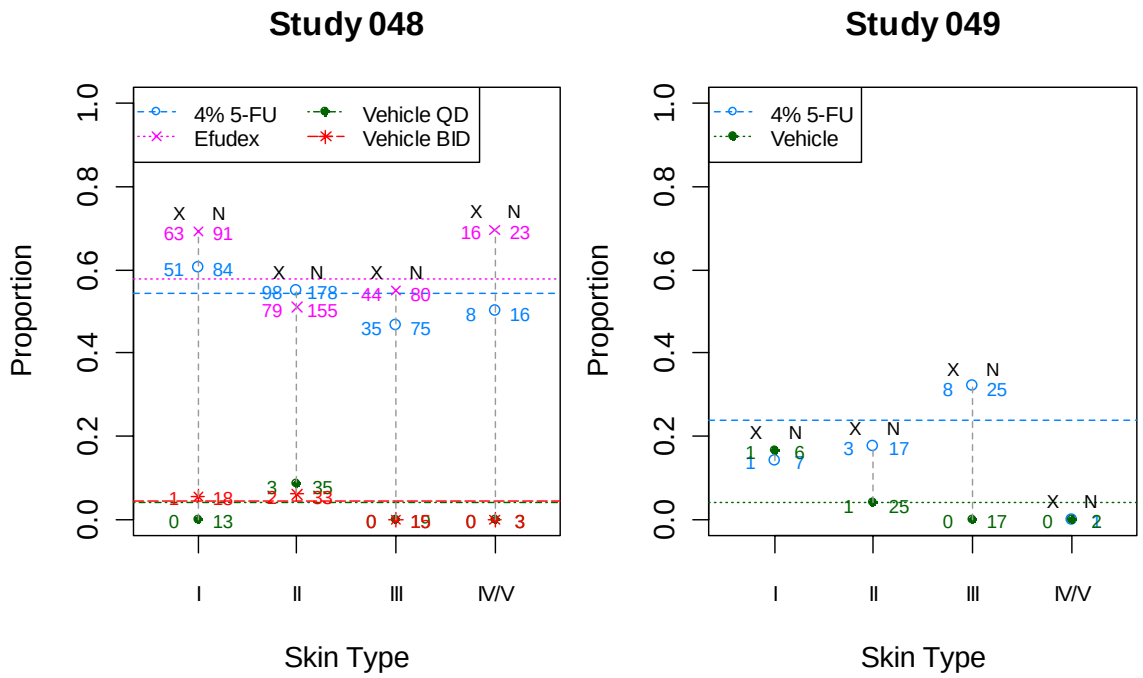


Note: X = Number cleared, N = Subgroup size

4.2 Other Special/Subgroup Populations

Although nearly all subjects were white and subgroup comparisons by race are not informative, subjects can be classified by Fitzpatrick skin type. No obvious differences in efficacy were noted by skin type. Clearance rates by skin type are presented in Figure 13.

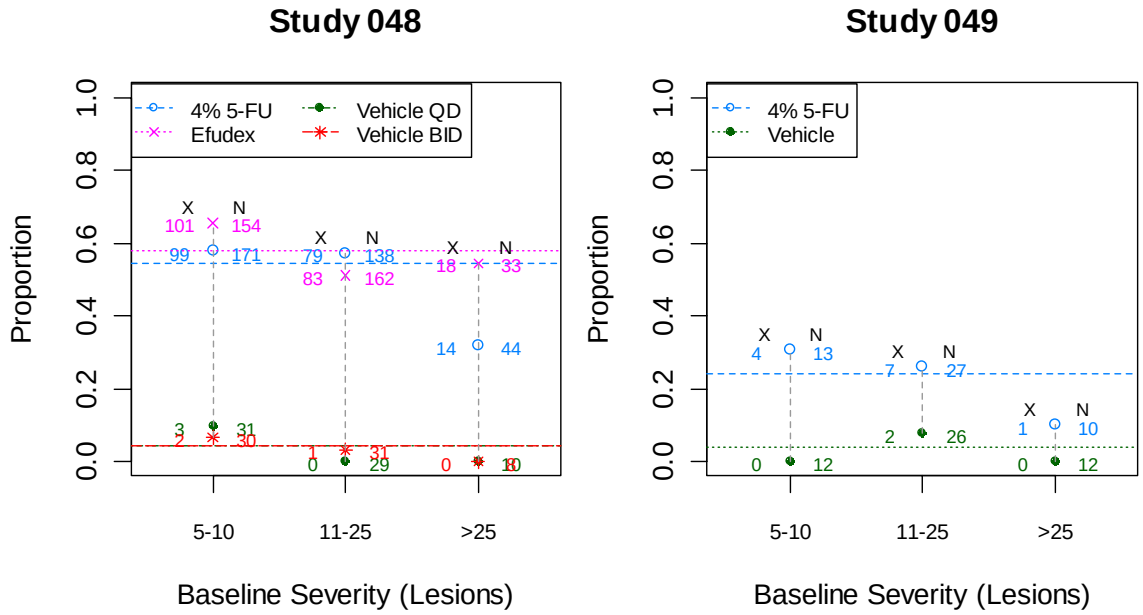
Figure 13 – Clearance Rates by Fitzpatrick Skin Type



Note: X = Number cleared, N = Subgroup size

The protocol defined three groupings for baseline severity for subgroup analysis: mild = 5 – 10 lesions, moderate = 11-25 lesions, and severe = more than 25 lesions. Although the number of subjects with more than 25 lesions was relatively small in each study, the 4% 5-FU clearance rate for this grouping was smaller than for the groupings of 5-10 and 11-25 lesions. The clearance rates for 5-10 and 11-25 lesions were similar for 4% 5-FU in each study. Clearance rates by baseline severity groupings are presented in Figure 14.

Figure 14 – Clearance Rates by Baseline Lesion Groupings



Note: X = Number cleared, N = Subgroup size

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Tradename (5-FU) 4% was superior to vehicle in both Phase 3 studies for the primary efficacy endpoint of 100% clearance of actinic keratoses at 4 weeks post-treatment. However, the treatment effect for the clearance rate was much higher in Study 048 than 049 (Study 048: 54% vs. 4%; Study 049: 24% vs. 4%). The reason for this difference is not clear, though it does not appear to be explained solely by differences in precision afforded by the respective sample sizes (Study 048 enrolled 353 4% 5-FU subjects while Study 049 enrolled 50 4% 5-FU subjects), or by differences in baseline lesion count (mean of 19.2 for Study 049 vs. 14.4 for Study 048 for 4% 5-FU subjects). Tradename (5-FU) 4% was also superior to vehicle in both studies for the secondary endpoints of 75% reduction in lesions and percent reduction in lesions. Study 048 was not able to demonstrate that 4% 5-FU was non-inferior to Efudex as the 97.5% lower confidence bounds for the treatment difference were -11.1% (ITT) and -12.8% (PP) with a pre-specified non-inferiority margin of 10%.

For subjects treated with 5-FU, lesion counts typically increased during the 4-week treatment period before resolving in the post-treatment period. Subjects who discontinued the study early from the 5-FU arms often had counts carried forward in the analysis that were higher than baseline. Since 5-FU subjects tend to worsen before they get better and many 5-FU subjects improved post-treatment even if they did not complete a full course of treatment, while vehicle subjects tended to remain stable around their

baseline values during and post-treatment, an LOCF analysis appears to be a fairly conservative way of handling missing data.

Many 5-FU subjects could not be assessed for lesion counts during treatment either due to skin reactions such as erythema or inflammation, or because the lesions were too numerous to count. Approximately 1/4 of 4% 5-FU subjects in Study 048 and 1/2 of 4% 5-FU subjects in Study 049 did not have lesion counts done at Week 4 due to such reasons. Lesion counts for vehicle subjects were typically stable during the treatment and post-treatment periods.

5.2 Conclusions and Recommendations

Tradename (5-fluorouracil) cream 4% has demonstrated superiority to its vehicle in the treatment of actinic keratoses in Studies 048 ($p < 0.001$) and 049 ($p=0.004$). In the clinical studies, Tradename (5-fluorouracil) cream 4% was applied once daily for 4 weeks by subjects with at least 5 actinic keratoses on the face, scalp, or ears. The primary efficacy endpoint was 100% clearance of lesions 4 weeks post-treatment. The test product was not shown to be non-inferior to the listed drug Efudex (97.5% lower confidence bounds of -11.1% (ITT) and -12.8% (PP) with a pre-specified non-inferiority margin of 10%) in Study 048, however efficacy can be established due to the demonstration that 4% 5-FU is superior to its vehicle in two studies.

Most 5-FU subjects experienced adverse events during the treatment period such as erythema (99%), scaling/dryness (95%), crusting (87%), pruritus (85%), stinging/burning (87%), edema (69%), and erosions (68%). These events were actively assessed during treatment. Many of these events were severe.

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