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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION

NEW DRUG APPLICATION

CLINICAL STUDIES

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Indication(s): Actinic Keratoses
Applicant: Graceway
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1 Executive Summary

1.1 Conclusions and Recommendations

Imiquimod cream 3.75% applied once daily to the face or scalp in two 2-week cycles (separated by a 2-week no treatment period) was superior to vehicle in the treatment of actinic keratoses (AK) in two studies ($p < 0.001$, statistically significant after adjusting for multiplicity). The studies enrolled subjects with 5 to 20 visible or palpable AKs in an area that exceeded 25 cm² on either the face or balding scalp. The treatment arms were 3.75% imiquimod, 2.5% imiquimod, and vehicle. The primary efficacy endpoint was complete clearance of lesions in the treatment area 8 weeks post-treatment (Week 14). See Table 1. The studies also demonstrated that imiquimod 2.5% cream was superior to vehicle for the same treatment regimen in two studies. The 3.75% cream had slightly higher observed clearance rates than the 2.5% cream. The secondary analyses of the AK lesion counts ($\geq 75\%$ clearance and percent reduction in lesions) also demonstrated statistical significance at Week 14. Lesion counts generally increased during active treatment periods, and usually returned to baseline levels between the two treatment periods.

Table 1 - Complete Clearance Rates 8 Weeks Post-Treatment

| Study | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|-------|-------------------|--------------------|--------------|
| 0702 | 19/81 (23.5%) | 21/81 (25.9%) | 2/80 (2.5%) |
| 0704 | 30/79 (38.0%) | 36/79 (45.6%) | 8/79 (10.1%) |

Note: all p-values versus vehicle were < 0.001 and are significant under Hochberg's method.

The local skin reactions of erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration were actively assessed during and after treatment. All of these events increased during active treatment with imiquimod, and returned to baseline levels after treatment.

1.2 Brief Overview of Clinical Studies

The applicant currently markets imiquimod 5% cream (Aldara) for the treatment of AK with a treatment regimen of two times per week for 16 weeks to a defined treatment area (approximately 25 cm²) on the face or scalp. In the current development program, which consisted of four studies, the applicant evaluated two new dosage regimens (daily treatment for two 2-week cycles with 2 weeks off between, and daily treatment for two 3-week cycles with 3 weeks off between). For each dosage regimen the applicant evaluated 2.5% and 3.75% imiquimod cream and vehicle. An overview of the clinical studies in the development program is presented in Table 2. All studies were of the same design and the primary efficacy endpoint was complete clearance of AK lesions 8 weeks post-treatment. The applicant is seeking approval for 3.75% imiquimod using the 2-week cycle regimen. Therefore, this review will focus on the 2-week cycle studies (0702 and 0704), with only brief results from the 3-week cycle studies when necessary to provide context or supportive information.

Table 2 – Clinical Study Program for 3.75% Imiquimod Cream

| Study | Regimen | Treatment Arms | No. of Subjects |
|-----------|----------------------------|-----------------------|-----------------|
| GW01-0702 | Daily for 2 weeks / | 2.5% imiquimod cream | 81 |
| | No treatment for 2 weeks / | 3.75% imiquimod cream | 81 |
| | Daily for 2 weeks | Vehicle | 80 |
| GW01-0704 | Daily for 2 weeks / | 2.5% imiquimod cream | 79 |
| | No treatment for 2 weeks / | 3.75% imiquimod cream | 79 |
| | Daily for 2 weeks | Vehicle | 79 |
| GW01-0703 | Daily for 3 weeks / | 2.5% imiquimod cream | 82 |
| | No treatment for 3 weeks / | 3.75% imiquimod cream | 80 |
| | Daily for 3 weeks | Vehicle | 78 |
| GW01-0705 | Daily for 3 weeks / | 2.5% imiquimod cream | 82 |
| | No treatment for 3 weeks / | 3.75% imiquimod cream | 82 |
| | Daily for 3 weeks | Vehicle | 86 |

1.3 Statistical Issues and Findings

The applicant has demonstrated that imiquimod cream 3.75% applied once daily to the face or scalp in two 2-week cycles is superior to vehicle in the treatment of AK in two studies. All imiquimod regimens evaluated in the clinical studies were superior to vehicle (Table 3) in the complete clearance or lesions. The 3.75% cream had slightly higher clearance rates than the 2.5% cream in all studies.

Table 3 – Complete Clearance Rates 8 Weeks Post-Treatment (ITT)

| | Study | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|---------------------------------|-------|-------------------|--------------------|------------|
| 2-Week Cycle Studies | 0702 | 19/81 (24%) | 21/81 (26%) | 2/80 (3%) |
| | 0704 | 30/79 (38%) | 36/79 (46%) | 8/79 (10%) |
| 3-Week Cycle Studies | 0703 | 19/82 (23%) | 26/80 (33%) | 4/78 (5%) |
| | 0705 | 22/82 (27%) | 29/82 (35%) | 5/86 (6%) |

Note: all p-values for imiquimod versus vehicle are <0.001 and are significant using Hochberg's procedure.

For the 2-week cycle regimen, the response rates observed in Study 0704 were somewhat higher than those observed in Study 0702. Exploratory analyses based on baseline or demographic characteristics or treatment compliance did not identify any reasons for the difference. The clearance rates for the 3-week cycle studies fell between those observed in the two 2-week cycle studies.

When clearance rates are analyzed by gender, although males had higher response rates using 3.75% imiquimod versus 2.5% imiquimod, females had higher response rates using 2.5% imiquimod. This was noted in both 2-week cycle studies. The number of female subjects was relatively small, however. See Table 4. The higher response rates observed in female subjects using 2.5% imiquimod was not replicated in the 3-week cycle studies, where no gender effect was observed. Because of the relatively small number of female

subjects in the studies, it is not clear whether the observed interaction could be generalized to a broader population.

Table 4 – Complete Clearance Rates by Gender

| Study | Gender | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|-------|--------|-------------------|--------------------|------------|
| 0702 | Male | 8/59 (14%) | 18/69 (26%) | 2/70 (3%) |
| | Female | 11/22 (50%) | 3/12 (25%) | 0/10 (0) |
| 0704 | Male | 21/68 (31%) | 28/63 (44%) | 4/60 (7%) |
| | Female | 9/11 (82%) | 8/16 (50%) | 4/19 (21%) |

The 3.75% cream also had slightly higher rates of adverse events than the 2.5% cream (47-49% vs. 43-44%) in Studies 0702 and 0704. Subjects who could not tolerate the irritating effects of treatment were permitted to take rest periods. Subjects using the 3.75% cream also had more and longer rest periods than subjects using the 2.5% cream, particularly in the second treatment cycle (9-13% of subjects for an average of 5.3 to 8.2 days vs. 6-8% of subjects for an average of 2.6 to 4.3 days).

One investigator in Study 0704 had problems with the randomization of 5 out of 15 subjects enrolled at the site. Four of the cases stemmed from the site having insufficient treatment kits on hand for the IVRS to appropriately assign treatment. The investigator issued treatment kits from the stock on hand, rather than wait for additional kits to arrive and then receive the allocation from the IVRS.

2 Introduction

2.1 Overview

The applicant is seeking approval for imiquimod cream 3.75% for the treatment of actinic keratoses (AK). The proposed treatment regimen is to apply treatment once daily to the entire face or balding scalp for two 2-week treatment cycles separated by a 2-week no-treatment period. The applicant currently markets imiquimod cream 5% under the tradename Aldara. Aldara 5% is indicated for the treatment of actinic keratoses (AK), superficial basal cell carcinoma, and genital warts. The full AK indication for Aldara 5% is “for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults.”

The treatment regimen for Aldara 5% in the treatment of AK is to apply Aldara cream two times per week for 16 weeks to a defined treatment area on the face or scalp (but not both concurrently). The treatment area is defined as one contiguous area of approximately 25 cm² (e.g. 5 cm × 5 cm) on the face **or** the scalp.

The applicant wanted to develop an alternate formulation and treatment regimen for imiquimod cream that could be applied daily, rather than twice a week, and to the entire face or scalp, rather than to a 25 cm² area. To this end, the applicant investigated four treatment regimens

- 2.5% imiquimod cream applied once daily for 2 weeks, followed by a 2-week rest period, and then followed by an additional 2-week period of once daily treatment
- 3.75% imiquimod cream applied once daily for 2 weeks, followed by a 2-week rest period, and then followed by an additional 2-week period of once daily treatment
- 2.5% imiquimod cream applied once daily for 3 weeks, followed by a 3-week rest period, and then followed by an additional 3-week period of once daily treatment
- 3.75% imiquimod cream applied once daily for 3 weeks, followed by a 3-week rest period, and then followed by an additional 3-week period of once daily treatment

The applicant conducted all dose-ranging in Phase 3 studies. The various treatment regimens were evaluated in four 3-arm clinical studies. Studies 0702 and 0704 evaluated 2.5% imiquimod, 3.75% imiquimod, and vehicle in the 2-week cycle regimen, while Studies 0703 and 0705 evaluated 2.5% imiquimod, 3.75% imiquimod, and vehicle in the 3-week cycle regimen. During development the Agency recommended that the applicant conduct dose-ranging studies prior to embarking on Phase 3 studies to limit the number of doses evaluated in Phase 3 and to provide comparisons of the 2-week regimens and 3-week regimens within the same study. See the minutes from meetings held on 7/27/2007 (IND 30,432) and 10/31/2007 (IND 49,480). This review will focus on the 2-week cycle studies 0702 and 0704, with brief discussion of the 3-week cycle studies 0703 and 0705.

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 in hybrid CTD electronic/paper format. The datasets used in this review are archived at \\Fds\swa150\none\ctd\N22483\N_000\2008-12-18\m5\datasets.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

The applicant conducted four vehicle-controlled Phase 3 studies, two evaluating the 2-week cycle regimen and two evaluating the 3-week cycle regimen. This review will focus on the 2-week cycle studies, and will briefly present the results of the 3-week cycle studies when necessary to provide context for dose-response.

3.1.1 Study Design

Studies GW01-0702 and GW01-0704 were randomized, double-blind studies of 2.5% imiquimod, 3.75% imiquimod, and vehicle cream in the treatment of AK of the face or scalp. At baseline, subjects were to have 5 to 20 visible or palpable AKs in an area that exceeded 25 cm² on either the face or balding scalp. Subjects applied treatment once daily in a 2-week cycle: two weeks on, two weeks off (no treatment period), two weeks on. Subjects applied treatment to either the entire face or balding scalp, but not both. Subjects applied treatment prior to normal sleeping hours and removed approximately 8 hours later. The primary efficacy endpoint was complete clearance of lesions in the treatment area 8 weeks post-treatment (Week 14). The secondary efficacy variables were

partial clearance of lesions (at least 75% reduction) at Week 14 and the percent change in lesions from baseline to Week 14.

The efficacy endpoints were analyzed with a Cochran-Mantel-Haenszel test stratified on center. Hochberg's procedure was used to control for multiplicity due to multiple doses. That is, if the least significant (larger p-value) dose is significant at 0.05 then both doses are declared significant, otherwise if the larger p-value is larger than 0.05 but the smaller p-value is less than 0.025, then the dose associated with the smaller p-value is declared significant. The primary method of handling missing data was last observation carried forward (LOCF), with taking missing values as failures used as a sensitivity analysis. The ITT population was defined as all randomized subjects. The per protocol population excluded subjects who failed to meet the inclusion/exclusion criteria, took restricted medications, did not adhere to the visit schedule, or were non-compliant with study treatment.

Studies GW01-0703 and GW01-0705 were identical to studies 0702 and 0704 except that they evaluated a 3-week cycle regimen (three weeks on, three weeks off, three weeks on), and that the 8-week post-treatment visit occurred on Week 17.

3.1.2 Subject Disposition

Study 0702 enrolled 242 subjects (81 to 2.5% imiquimod, 81 to 3.75% imiquimod, and 80 to vehicle). Approximately 6% of subjects discontinued the study before Week 14. The 3.75% imiquimod arm had the highest rate of discontinuation (9%). The most common reasons for discontinuation were subject's request, safety reasons, and lost to follow-up. Table 5 displays the reasons for discontinuation and any comments by the investigator regarding the safety reasons or subject request reasons. Not all discontinuing subjects had investigator comments.

Table 5 – Disposition of Subjects (Study 0702)

| | 2.5% Imiq. | 3.75% Imiq. | Vehicle |
|------------------------------------|--------------------------------------------|---------------------------------------------------------------------------|---------------------------------------|
| Subjects | 81 | 81 | 80 |
| Randomized | | | |
| Completed study | 78 (96%) | 74 (91%) | 75 (94%) |
| Discontinued study | 3 (4%) | 7 (9%) | 5 (6%) |
| <i>Reasons for discontinuation</i> | | | |
| Safety reasons (AEs) | 1 (tachycardia/ angina/ elevated BP) | 1 (increased tremors due to Parkinson's) | 2 (a) (headache) (b) (migraine) |
| Subject's request (not AE) | 1 (unknown) | 3 (a) (time constraints) (b) (cosmetic appearance) (c) (unknown) | 2 (a) (unknown) (b) (unknown) |
| Noncompliance | 0 | 0 | 0 |
| Concomitant therapy | 0 | 1 | 0 |
| Lost to follow-up | 1 | 2 | 1 |
| Other (not AE) | 0 | 0 | 0 |

Study 0704 enrolled 237 subjects (79 to 2.5% imiquimod, 79 to 3.75% imiquimod, and 79 to vehicle). Approximately 5% of subjects discontinued the study before Week 14. All arms had similar discontinuation rates. The most common reason for discontinuation was subject request. Table 6 displays the reasons for discontinuation and any comments by the investigator regarding the safety reasons, subject request reasons, or ‘other’ reasons. Not all discontinuing subjects had investigator comments.

Table 6 – Disposition of Subjects (Study 0704)

| | 2.5% Imiq. | 3.75% Imiq. | Vehicle |
|------------------------------------|------------------|------------------------------------------------------------------|-------------------------------------|
| Subjects Randomized | 79 | 79 | 79 |
| Completed study | 76 (96%) | 75 (95%) | 75 (95%) |
| Discontinued study | 3 (4%) | 4 (5%) | 4 (5%) |
| <i>Reasons for discontinuation</i> | | | |
| Safety reasons (AEs) | 0 | 1 (headaches/ fatigue/ aching from waist up/ face pain) | 1 (tinnitus) |
| Subject’s request (not AE) | 1 (unknown) | 1 (severe local reaction) | 2 (a) (unknown) (b) (unknown) |
| Noncompliance | 0 | 1 | 0 |
| Concomitant therapy | 0 | 0 | 1 |
| Lost to follow-up | 1 | 0 | 0 |
| Other (not AE) | 1 (left town) | 1 (left town) | 0 |

3.1.3 Baseline Characteristics

Baseline demographics were generally balanced across treatment groups in Studies 0702 and 0704, though the gender groups were slightly imbalanced. About 80% of the subjects were male, ranging from 73% in the 2.5% imiquimod arm to 85-88% in the 3.75% and vehicle arms in Study 0702, and ranging from 76-86% in Study 0704. The average age was 63 to 65 years. All but one subject was white. About 6% of subjects in Study 0702 identified as Hispanic, though only one subject in Study 0704 was Hispanic. The majority of subjects had Fitzpatrick skin type of I – III. The baseline demographics are presented in Table 7 and Table 8.

Table 7 – Baseline Demographics (Study 0702)

| | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|------------------------------|--------------------|---------------------|-----------------|
| <i>Age (years)</i> | | | |
| Mean | 63.7 | 63.8 | 63.6 |
| Range | 43 - 88 | 36 - 89 | 42 - 83 |
| <i>Gender</i> | | | |
| Male | 59 (73%) | 69 (85%) | 70 (88%) |
| Female | 22 (27%) | 12 (15%) | 10 (13%) |
| <i>Ethnicity</i> | | | |
| Hispanic | 4 (5%) | 5 (6%) | 5 (6%) |
| Non-Hispanic | 77 (95%) | 76 (94%) | 75 (94%) |
| <i>Race</i> | | | |
| White | 81 (100%) | 81 (100%) | 80 (100%) |
| <i>Fitzpatrick Skin Type</i> | | | |
| I | 9 (11%) | 5 (6%) | 6 (8%) |
| II | 35 (43%) | 43 (53%) | 25 (31%) |
| III | 23 (28%) | 17 (21%) | 37 (46%) |
| IV | 11 (14%) | 15 (19%) | 11 (14%) |
| V | 3 (4%) | 1 (1%) | 1 (1%) |

Table 8 – Baseline Demographics (Study 0704)

| | 2.5% Imiq. N=79 | 3.75% Imiq. N=79 | Vehicle N=79 |
|------------------------------|--------------------|---------------------|-----------------|
| <i>Age (years)</i> | | | |
| Mean | 65.0 | 65.3 | 65.0 |
| Range | 39 - 90 | 36 - 86 | 46 - 89 |
| <i>Gender</i> | | | |
| Male | 68 (86%) | 63 (80%) | 60 (76%) |
| Female | 11 (14%) | 16 (20%) | 19 (24%) |
| <i>Ethnicity</i> | | | |
| Hispanic | 0 | 1 (1%) | 0 |
| Non-Hispanic | 79 (100%) | 78 (99%) | 79 (100%) |
| <i>Race</i> | | | |
| White | 79 (100%) | 79 (100%) | 78 (99%) |
| Am. Ind/AK Native | 0 | 0 | 1 (1%) |
| <i>Fitzpatrick Skin Type</i> | | | |
| I | 20 (25%) | 17 (22%) | 13 (16%) |
| II | 27 (34%) | 31 (39%) | 33 (42%) |
| III | 20 (25%) | 26 (33%) | 26 (33%) |
| IV | 11 (14%) | 5 (6%) | 5 (6%) |
| V | 1 (1%) | 0 | 2 (3%) |

For enrollment, subjects were to have 5 to 20 typical visible or palpable AK lesions in an area that exceeded 25 cm² on either the face or balding scalp. Approximately 70 to 75%

of subjects treated lesions on the face, while 25 to 30% treated lesions on the balding scalp. All subjects met the inclusion criterion of 5 to 20 lesions, except one subject enrolled with 29 lesions in Study 0704. See Table 9 and Table 10.

Table 9 – Baseline Disease Characteristics (Study 0702)

| | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|-----------------|--------------------|---------------------|-----------------|
| <i>Location</i> | | | |
| Face | 61 (75%) | 66 (81%) | 60 (75%) |
| Balding Scalp | 20 (25%) | 15 (19%) | 20 (25%) |
| <i>Lesions</i> | | | |
| Mean | 11.1 | 10.9 | 11.7 |
| Range | 5 - 20 | 5 - 20 | 5 - 20 |

Table 10 – Baseline Disease Characteristics (Study 0704)

| | 2.5% Imiq. N=79 | 3.75% Imiq. N=79 | Vehicle N=79 |
|-----------------|--------------------|---------------------|-----------------|
| <i>Location</i> | | | |
| Face | 56 (71%) | 55 (70%) | 59 (75%) |
| Balding Scalp | 23 (29%) | 24 (30%) | 20 (25%) |
| <i>Lesions</i> | | | |
| Mean | 10.8 | 11.2 | 10.8 |
| Range | 5 - 20 | 5 - 29 | 5 - 20 |

3.1.4 Primary Efficacy Results

Both imiquimod 2.5% and 3.75% were superior to vehicle in Studies 0702 and 0704 for the primary efficacy endpoint of complete clearance 8 weeks post-treatment (Week 14) ($p < 0.001$, significant under Hochberg's method). The complete clearance rates for all four studies (2-week cycle and 3-week cycle) 8 weeks post-treatment are presented in Table 11.

Table 11 – Complete Clearance Rates 8 Weeks Post-Treatment (ITT)

| | Study | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|-----------------------------------------------|-------|-------------------|--------------------|--------------|
| 2-Week Cycle Studies (Week 14) | 0702 | 19/81 (23.5%) | 21/81 (25.9%) | 2/80 (2.5%) |
| | | <0.001 | <0.001 | |
| | 0704 | 30/79 (38.0%) | 36/79 (45.6%) | 8/79 (10.1%) |
| | | <0.001 | <0.001 | |
| 3-Week Cycle Studies (Week 17) | 0703 | 19/82 (23.2%) | 26/80 (32.5%) | 4/78 (5.1%) |
| | | <0.001 | <0.001 | |
| | 0705 | 22/82 (26.8%) | 29/82 (35.4%) | 5/86 (5.8%) |
| | | <0.001 | <0.001 | |

P-values are versus vehicle and are evaluated using Hochberg's procedure.

In each study the observed clearance rate for the 3.75% formulation was slightly higher than for the 2.5% formulation (26% vs. 23% in 0702 and 46% vs. 38% in 0704 and similarly in the 3-week cycle studies). In Study 0702 the complete clearance rates are 8 to 20% higher in Study 0704 than in 0702, whereas the response rates in the 3-week cycle studies were more consistent with each other. The response rate differences between Study 0702 and 0704 will be more fully explored in Section 3.1.9. The per protocol results are similar to the ITT results and are presented in Table 12 for Studies 0702 and 0704.

Table 12 - Complete Clearance Rates 8 Weeks Post-Treatment (PP)

| Study | Imiquimod | Imiquimod | Vehicle |
|-------|-------------|-------------|------------|
| | 2.5% | 3.75% | |
| 0702 | 17/75 (23%) | 20/73 (27%) | 1/70 (1%) |
| 0704 | 25/67 (37%) | 34/68 (50%) | 7/72 (10%) |

3.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints were partial clearance (at least 75% reduction from baseline) and the percent change in lesions at Week 14. These analyses of the lesions produced similar results to the primary analysis of complete clearance. See Table 13 and Table 14.

Table 13 – Partial ($\geq 75\%$) Clearance Rates 8 Weeks Post-Treatment (ITT)

| Study | Imiquimod | Imiquimod | Vehicle |
|-------|-------------|-------------|-------------|
| | 2.5% | 3.75% | |
| 0702 | 34/81 (42%) | 37/81 (46%) | 15/80 (19%) |
| 0704 | 43/79 (54%) | 58/79 (73%) | 21/79 (27%) |

Note: all p-values versus vehicle were ≤ 0.001 .

Table 14 – Change and Percent Change from Baseline (ITT)

| 0702 | 2.5% Imiq. | | 3.75% Imiq. | | Vehicle | |
|-------------|-------------|------------|-------------|------------|-------------|------------|
| | N=81 | | N=81 | | N=80 | |
| | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> |
| Baseline | 11.1 | 10 | 10.9 | 9 | 11.7 | 10 |
| Change | -5.5 | -6 | -6.8 | -7 | -2.8 | -2 |
| % Change | -53% | -60% | -60% | -73% | -23% | -21% |
| 0704 | 2.5% Imiq. | | 3.75% Imiq. | | Vehicle | |
| | N=79 | | N=79 | | N=79 | |
| | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> |
| Baseline | 10.8 | 10 | 11.2 | 11 | 10.8 | 10 |
| Change | -6.7 | -7 | -8.5 | -9 | -3.4 | -3 |
| % Change | -66% | -77% | -78% | -91% | -33% | -30% |

Note: all p-values for mean percent change for imiquimod versus vehicle were ≤ 0.001 .

3.1.6 Lesions over Time

Investigators counted the number of AK lesions in the treatment area at each visit. In some cases, investigators rated subjects as having ‘indeterminate’ lesion counts when the

lesions were confluent and not easily counted. Up to 23% of imiquimod subjects were classified as having ‘indeterminate’ lesion counts at a visit, particularly at the end of the first treatment cycle (Week 2). See Table 15 and Table 16.

Table 15 – Number of ‘Indeterminate’ Lesion Counts and Missing Observations by Week (Study 0702)

| Week | Value | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|------|---------------|--------------------|---------------------|-----------------|
| 1 | Indeterminate | 1 (1%) | 3 (4%) | -- |
| | Missing | -- | 1 (1%) | 2 (2%) |
| 2 | Indeterminate | 7 (9%) | 15 (19%) | -- |
| | Missing | 2 (2%) | 1 (1%) | 2 (2%) |
| 4 | Indeterminate | -- | 1 (1%) | -- |
| | Missing | 2 (2%) | 4 (5%) | 4 (5%) |
| 5 | Indeterminate | 3 (4%) | 7 (9%) | -- |
| | Missing | 2 (2%) | 6 (7%) | 8 (10%) |
| 6 | Indeterminate | 10 (12%) | 17 (21%) | -- |
| | Missing | 1 (1%) | 5 (6%) | 6 (7%) |
| 10 | Indeterminate | 1 (1%) | -- | -- |
| | Missing | 1 (1%) | 6 (7%) | 5 (6%) |
| 14 | Indeterminate | -- | 1 (1%) | -- |
| | Missing | 2 (2%) | 4 (5%) | 3 (4%) |

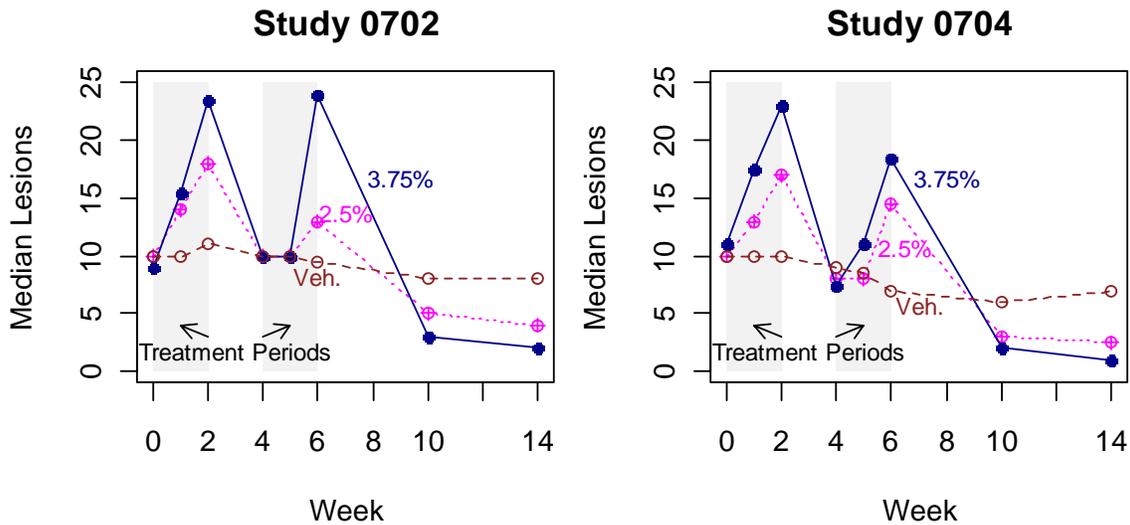
Table 16 – Number of ‘Indeterminate’ Lesion Counts and Missing Observations by Week (Study 0704)

| Week | Value | 2.5% Imiq. N=79 | 3.75% Imiq. N=79 | Vehicle N=79 |
|------|---------------|--------------------|---------------------|-----------------|
| 1 | Indeterminate | 5 (6%) | 8 (10%) | -- |
| | Missing | 4 (5%) | 3 (4%) | 5 (6%) |
| 2 | Indeterminate | 17 (22%) | 18 (23%) | -- |
| | Missing | -- | 5 (6%) | 2 (3%) |
| 4 | Indeterminate | 2 (3%) | 4 (5%) | -- |
| | Missing | 4 (5%) | 5 (6%) | 3 (4%) |
| 5 | Indeterminate | 6 (8%) | 6 (8%) | -- |
| | Missing | 6 (8%) | 9 (11%) | 11 (14%) |
| 6 | Indeterminate | 9 (11%) | 12 (15%) | -- |
| | Missing | 1 (1%) | 5 (6%) | 2 (3%) |
| 10 | Indeterminate | -- | -- | -- |
| | Missing | 2 (3%) | 5 (6%) | 4 (5%) |
| 14 | Indeterminate | -- | 1 (1%) | -- |
| | Missing | 1 (1%) | -- | -- |

While on active treatment with imiquimod, the number of observed AK lesions frequently increased over the baseline level. During the rest period, the observed number of lesions typically returned to baseline levels. The median numbers of lesions over time

are presented in Figure 1. For the purpose of calculating medians, ‘indeterminate’ counts are considered to be greater than the median for that visit. Missing observations are ignored. Note that this handling of ‘indeterminate’ counts is slightly different than the applicant’s; the applicant used LOCF to handle indeterminate and missing counts.

Figure 1 – Median Lesions over Time (Studies 0702 and 0704)



3.1.7 Efficacy by Center

Within each study, the complete clearance rates for each center are fairly similar, with no centers dominating the results. Centers in Study 0704 generally had higher response rates than those in Study 0702. At most centers of at least moderate size, the clearance rate for imiquimod 3.75% was higher than for imiquimod 2.5%. However, as the overall response rate for imiquimod 3.75% was not much different than for imiquimod 2.5%, some centers had higher response rates on the 2.5% arm. See Figure 2 and Figure 3.

Figure 2 – Complete Clearance Rate by Center (Study 0702)

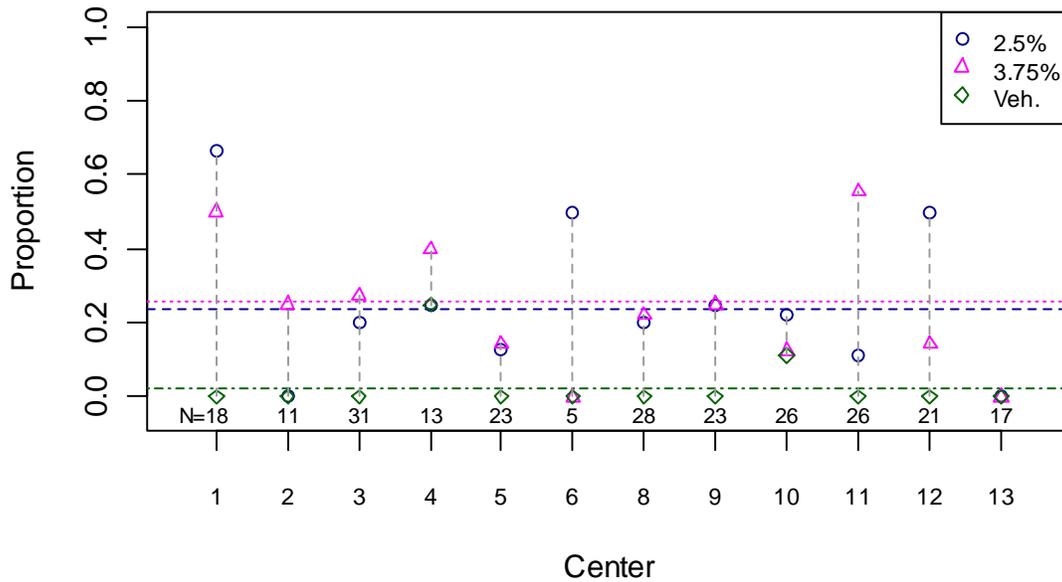
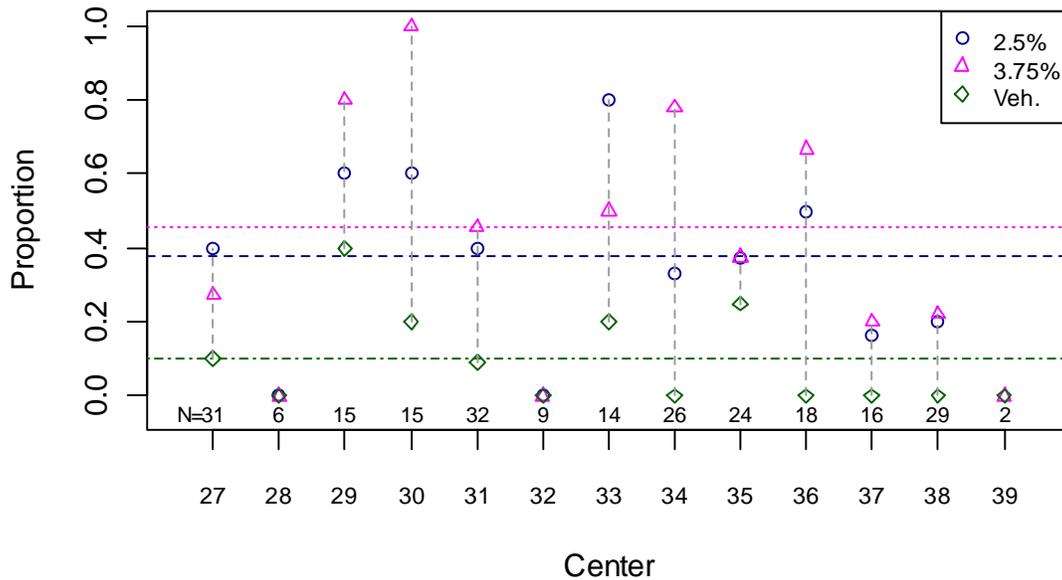


Figure 3 – Complete Clearance Rate by Center (Study 0704)



3.1.8 Randomization Irregularities

One site in Study 0704 (Center 30) reported problems with randomization using the IVRS. According to the applicant, if a study center did not have at least one kit of each of the three treatments on hand, the IVRS was designed not to assign a randomized kit number to the investigator until the supplies had been refilled. In four cases Center 30 was unable to get a randomized kit number through the IVRS because insufficient kits were on hand. However, rather than delaying randomization for these subjects until new shipments of kits had arrived as the system required, the investigator elected to select kits

from the remaining stock on hand for the subjects. The IVRS permitted 8 randomizations on 2/18/2008 and 2/25/2008 before the supplies ran low and the system refused additional allocations:

- Vehicle – 4
- 3.75% imiquimod – 2
- 2.5% imiquimod - 2

The site apparently ran out of vehicle kits. However, the site randomized two additional subjects on 2/25/2008 by selecting from the remaining kits at the site; one subject received 3.75% imiquimod and one received 2.5% imiquimod. The site next attempted to randomize four subjects on 3/3/2008. The first two subjects on this date both were randomized to 3.75% imiquimod before the system refused additional allocations. This time the site apparently ran out of 3.75% kits. Again the site selected kits for two additional subjects after not being able to get an allocation from the IVRS, one each to 2.5% imiquimod and vehicle.

In addition, during one randomization, Center 30 was unable to decipher the kit allocation due to static on the line, so again the site selected a treatment kit for the subject. In this case, the allocated kit was the same treatment (3.75%) as the one actually assigned by the IVRS. One other subject in Study 0704 was also misrandomized. At Center 27, although the site received the correct kit number from the IVRS, the wrong kit was inadvertently distributed to the subject. This subject had been randomized to 2.5% imiquimod but was issued 3.75% imiquimod. All subjects in Study 0702 received the correct treatment kits.

As can be seen from Figure 3, Center 30 had the highest complete clearance rate for 3.75% imiquimod (5/5, 100%) among the centers. Due to the fact that the site had irregularities with the randomization of one-third of its subjects and high response rates, it may be appropriate to consider a sensitivity analysis which removes the subjects from Center 30. Removal of the subjects from Center 30 reduces the response rates slightly on all 3 arms, but the overall conclusions still support the efficacy of imiquimod. See Table 17.

Table 17 – Study 0704 Complete Clearance Rates Excluding Center 30

| | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|------------------------|-------------------------|-------------------------|-------------|
| 0704 (excl. Center 30) | 27/74 (36.5%) <0.001 | 31/74 (41.9%) <0.001 | 7/74 (9.5%) |
| Center 30 | 3/5 (60%) | 5/5 (100%) | 1/5 (20%) |

The applicant has submitted the Project Requirements Specification for the IVRS that was finalized before the study. The document specifies how the system would handle kits allocated without a response from the IVRS. The specifications state that

- the system would manually allocate next randomization number
- the subject would continue in the trial and appropriate database updates would be performed, and

- the treatment kit assigned to the subject will be marked with a special code and would not be available for further assignment
(pg. 102 of 159 of NDA amendment N-000-B2, stamp date 4/2/2009)

Once the system was updated with information that kits had been allocated, this information appears to have some impact on future randomizations ('system manually allocated next randomization number'). Thus, while sensitivity analyses are important to understand the impact of the misrandomized subjects on the results, it is not clear that an analysis that removes the subjects is necessarily more appropriate than one that includes the subjects.

3.1.9 Difference in Response Rates between Studies

Study 0704 had higher response rates for all treatments than Study 0702. Analyses by center (Figure 2 and Figure 3) and various other subgroups (Figure 6 through Figure 10) do not identify any factors that might explain the difference. The complete clearance rate at Week 14 reflects one aspect of the distribution of the AK counts—the proportion of subjects with a count of 0. The mean and median AK counts (using LOCF imputation for missing data) at baseline and Week 14 are presented in Table 18. For all treatment arms, the mean Week 14 AK counts in Study 0704 are approximately 1.5 lesions lower than the corresponding means in Study 0702. Thus, the differences observed between Studies 0702 and 0704 regarding the complete clearance rates, also correspond to differences in Week 14 mean counts. There is no clear explanation for the observed differences in the study results.

Table 18 – Baseline and Week 14 AK Counts

| 0702 | 2.5% Imiq. N=81 | | 3.75% Imiq. N=81 | | Vehicle N=80 | |
|-------------|--------------------|------------|---------------------|------------|-----------------|------------|
| | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> |
| Baseline | 11.1 | 10 | 10.9 | 9 | 11.7 | 10 |
| Week 14 | 5.6 | 4 | 4.1 | 3 | 8.9 | 8 |
| 0704 | 2.5% Imiq. N=79 | | 3.75% Imiq. N=79 | | Vehicle N=79 | |
| | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> | <i>Mean</i> | <i>Med</i> |
| Baseline | 10.8 | 10 | 11.2 | 11 | 10.8 | 10 |
| Week 14 | 4.1 | 2 | 2.6 | 1 | 7.4 | 7 |

Note that variation in complete clearance rates between studies has also been observed in other development programs for topical AK treatments. For example, in two studies for imiquimod 5% cream (3 times weekly for 16 weeks) one study had a clearance rate for imiquimod of 41% vs. 56% in the other study (see Statistical Review by Kathleen Fritsch, PhD dated 2/23/2004 for NDA 20-723). Also, in two studies for 5-fluorouracil 4% (once daily for 4 weeks), one study had a clearance rate for 5-fluorouracil of 24% vs. 54% in the other study (see Statistical Review by Kathleen Fritsch, PhD dated 4/4/2008 for NDA 22-259). Thus the situation of differential response rates between studies for topical treatment of AKs is not limited to this application.

3.2 Evaluation of Safety

3.2.1 Extent of Exposure

Subjects on all three treatment arms had similar numbers of applications in the first treatment cycle (mean of 13.4 to 13.9) in both studies. In the second cycle, subjects in the 3.75% imiquimod arm had an average of about one fewer application (12.5 vs. 13.4 to 13.6) than subjects on the 2.5% imiquimod arm. See Table 19 and Table 20.

Table 19 – Mean number of Treatment Applications by Cycle (Study 0702)

| Applications | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|--------------|--------------------|---------------------|-----------------|
| Cycle 1 | 13.6 | 13.7 | 13.6 |
| Cycle 2 | 13.6 | 12.5 | 12.8 |
| Overall | 27.2 | 26.2 | 26.4 |

Table 20 – Mean number of Treatment Applications by Cycle (Study 0704)

| Applications | 2.5% Imiq. N=79 | 3.75% Imiq. N=78* | Vehicle N=79 |
|--------------|--------------------|----------------------|-----------------|
| Cycle 1 | 13.9 | 13.4 | 13.9 |
| Cycle 2 | 13.4 | 12.5 | 13.2 |
| Overall | 27.3 | 26.1 | 27.1 |

*One subject had unknown number of applications and is excluded.

Subjects with local skin reactions were permitted to take rest periods from treatment. Approximately 6-8% of 2.5% imiquimod subjects and 9-13% of 3.75% imiquimod subjects took rest periods. No vehicle subjects required rest periods. Among subjects requiring a rest period during the first cycle, the average start time was around Day 9 to 10 for both imiquimod arms, with the earliest onset of Day 6. During the first treatment cycle, subjects needing rest periods typically missed 2 to 4 days of treatment. Among subjects needing rest periods in the second treatment cycle, the rest periods were a little longer on average, 4 to 9 days. Overall, slightly more subjects in the 3.75% arm required rest periods than in the 2.5% arm, and the rest periods were slightly longer. See Table 21 and Table 22.

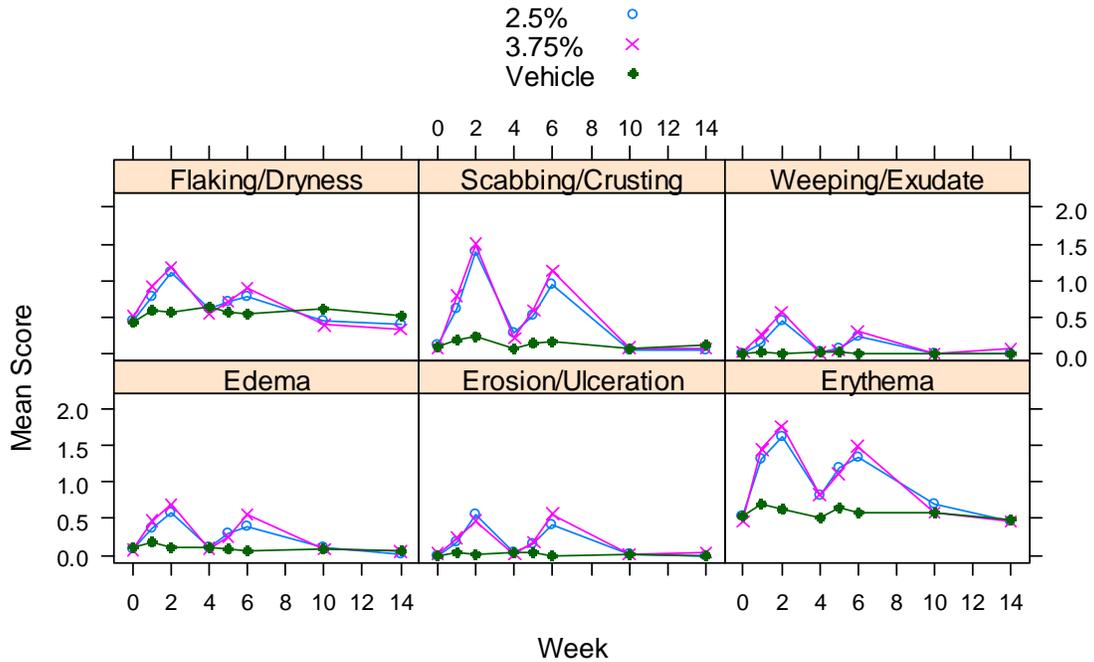
Table 21 – Rest Periods by Cycle (Study 0702)

| | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|---------------------------------------------------------------|--------------------|---------------------|-----------------|
| Subjects Requiring Rest Periods | | | |
| Cycle 1 | 5/81 (6%) | 3/81 (4%) | 0/80 (0%) |
| Cycle 2 | 0/80 (0%) | 4/76 (5%) | 0/76 (0%) |
| Overall | 5/81 (6%) | 7/81 (9%) | 0/80 (0%) |
| Mean (Range) of Dosing Days Missed Due to Rest Period | | | |
| Cycle 1 | 2.6 1 to 5 | 3.0 1 to 4 | -- |
| Cycle 2 | -- | 7.0 1 to 14 | -- |
| Overall | 2.6 1 to 5 | 5.3 1 to 14 | -- |
| Mean (Range) of Dosing Days Prior to First Rest Period | | | |
| Cycle 1 | 9.4 6 to 13 | 10 7 to 13 | -- |
| Cycle 2 | -- | 5.8 0 to 13 | -- |
| Overall | 9.4 6 to 13 | 15.6 7 to 27 | -- |

Table 22 – Rest Periods by Cycle (Study 0704)

| | 2.5% Imiq. N=79 | 3.75% Imiq. N=79 | Vehicle N=79 |
|---------------------------------------------------------------|--------------------|---------------------|-----------------|
| Subjects Requiring Rest Periods | | | |
| Cycle 1 | 4/79 (5%) | 7/79 (9%) | 0/79 (0%) |
| Cycle 2 | 3/78 (4%) | 6/76 (8%) | 0/77 (0%) |
| Overall | 6/79 (8%) | 10/79 (13%) | 0/79 (0%) |
| Mean (Range) of Dosing Days Missed Due to Rest Period | | | |
| Cycle 1 | 2.8 2 to 4 | 4.3 1 to 7 | -- |
| Cycle 2 | 5.0 3 to 8 | 8.7 2 to 14 | -- |
| Overall | 4.3 2 to 8 | 8.2 3 to 20 | -- |
| Mean (Range) of Dosing Days Prior to First Rest Period | | | |
| Cycle 1 | 9.8 7 to 12 | 9.7 7 to 13 | -- |
| Cycle 2 | 6.0 0 to 11 | 5.0 0 to 12 | -- |
| Overall | 12.3 7 to 21 | 12.8 7 to 25 | -- |

Figure 5 - Mean Local Skin Reaction Scores by Visit (Study 0704)



3.2.3 Adverse Events

Adverse event rates exhibited dose response; vehicle had the lowest rates (30-36%), followed by 2.5% imiquimod (43-44%) and 3.75% imiquimod (47-49%). The most common adverse events were headache, respiratory events (nasopharyngitis, upper respiratory tract infection, influenza-like illness), application site reactions, and arthralgia, fatigue, nausea, and dizziness. See Table 23 and Table 24.

Table 23 – Adverse Events (Study 0702)

| | 2.5% Imiq. N=81 | 3.75% Imiq. N=81 | Vehicle N=80 |
|---------------------------------------------------------|--------------------|---------------------|-----------------|
| Any Adverse Event | 35 (43%) | 40 (49%) | 29 (36%) |
| Any Treatment-Related Event | 10 (12%) | 13 (16%) | 4 (5%) |
| Any Application Site Reaction | 6 (7%) | 6 (7%) | 2 (3%) |
| Any Serious Adverse Event | 3 (4%) | 2 (3%) | 2 (3%) |
| Any Severe Adverse Event | 5 (6%) | 2 (3%) | 2 (3%) |
| Most Common Adverse Events (>3% in any group) | | | |
| Upper Resp. Tract Inf. | 3 (4%) | 4 (5%) | 5 (6%) |
| App. Site Pruritus | 3 (4%) | 2 (3%) | 1 (1%) |
| Headache | 2 (3%) | 1 (1%) | 3 (4%) |
| Oral Herpes | 4 (5%) | 0 | 0 |
| Pain | 0 | 3 (4%) | 0 |

Source: Table 14.3.3.1, pg 243, file gw01-0702.pdf

Table 24 – Adverse Events (Study 0704)

| | 2.5% Imiq. N=79 | 3.75% Imiq. N=79 | Vehicle N=79 |
|--------------------------------------------------|--------------------|---------------------|-----------------|
| Any Adverse Event | 35 (44%) | 37 (47%) | 24 (30%) |
| Any Treatment-Related Event | 9 (11%) | 18 (23%) | 0 (0%) |
| Any Application Site Reaction | 4 (5%) | 11 (14%) | 0 (0%) |
| Any Serious Adverse Event | 2 (3%) | 3 (4%) | 0 (0%) |
| Any Severe Adverse Event | 3 (4%) | 4 (5%) | 0 (0%) |
| Most Common Adverse Events (>3% in any group) | | | |
| Headache | 1 (1%) | 9 (11%) | 2 (3%) |
| Nasopharyngitis | 2 (3%) | 2 (3%) | 6 (8%) |
| App. Site Pruritus | 3 (4%) | 5 (6%) | 0 |
| App. Site Irritation | 2 (3%) | 4 (5%) | 0 |
| Arthralgia | 4 (5%) | 2 (3%) | 0 |
| Fatigue | 0 | 5 (6%) | 0 |
| Lymphadenopathy | 3 (4%) | 2 (3%) | 0 |
| Nausea | 0 | 5 (6%) | 0 |
| Dizziness | 0 | 4 (5%) | 0 |
| Influenza-like Illness | 3 (4%) | 1 (1%) | 0 |
| Pyrexia | 0 | 4 (5%) | 0 |
| App. Site Pain | 0 | 3 (4%) | 0 |

Source: Table 14.3.3.1, pg 245, file gw01-0704.pdf

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

In both Studies 0702 and 0704, the clearance rates for subjects using 3.75% imiquimod were similar for both male and female subjects, but for subjects using 2.5% imiquimod, female subjects had higher clearance rates than males (and also higher than subjects using 3.75% imiquimod). See Figure 6. The reason for this interaction is unknown, though the number of female subjects is fairly small. Because this pattern was observed in both 2-week cycle studies, the complete clearance rates by gender were also evaluated for the two 3-week cycle studies (Studies 0703 and 0705). The 3-week cycle studies did not demonstrate a greater effect of the 2.5% treatment in females (Figure 7). Therefore, unless there is a reason that 2.5% imiquimod would lead to better response in female subjects under the 2-week cycle regimen but not in the 3-week cycle regimen, the finding may be due to chance. See also additional discussion of the gender finding in 4.2.2.

Figure 6 – Complete Clearance Rates by Gender

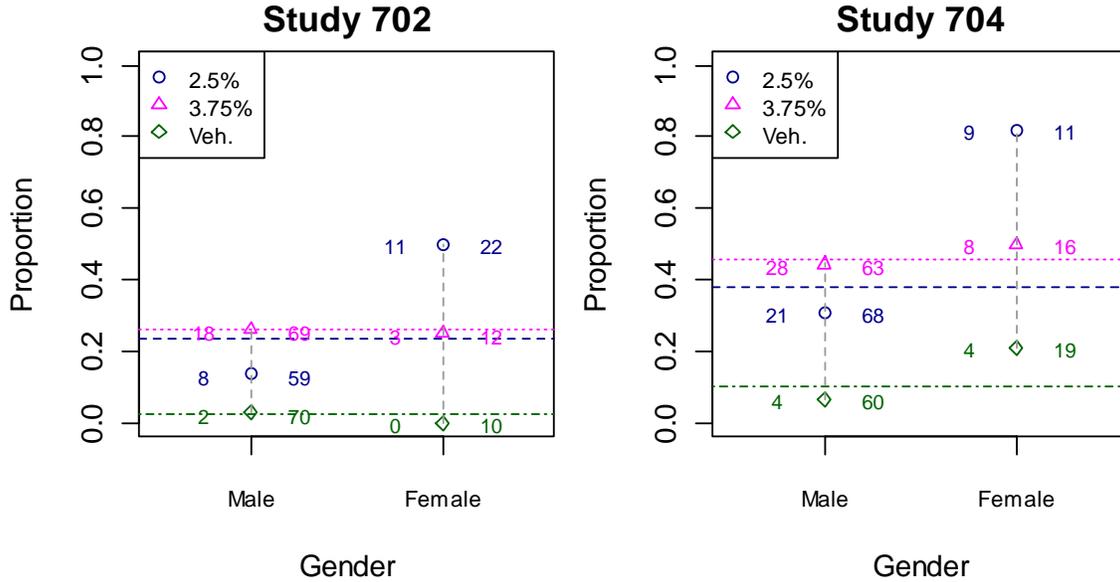
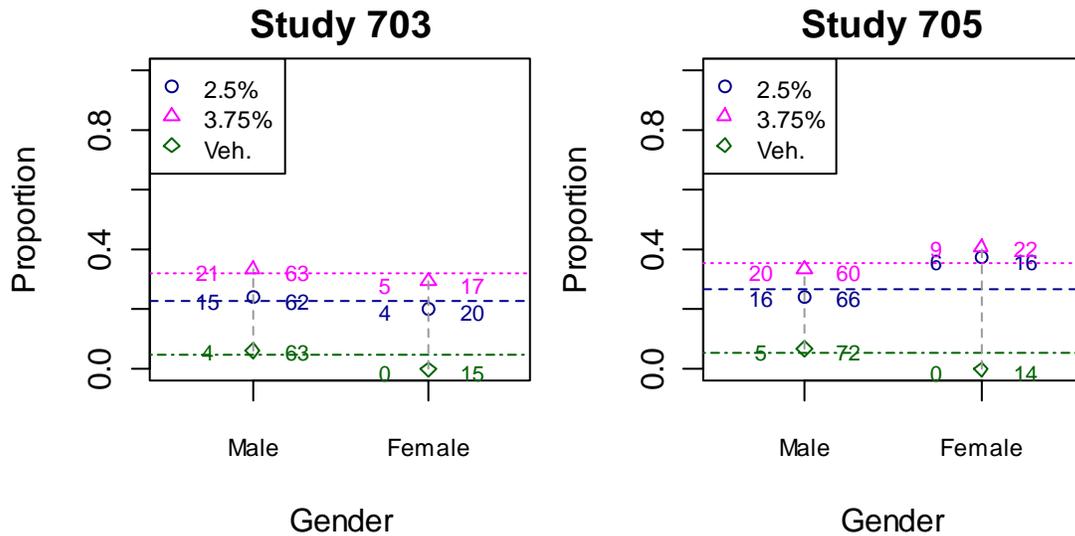
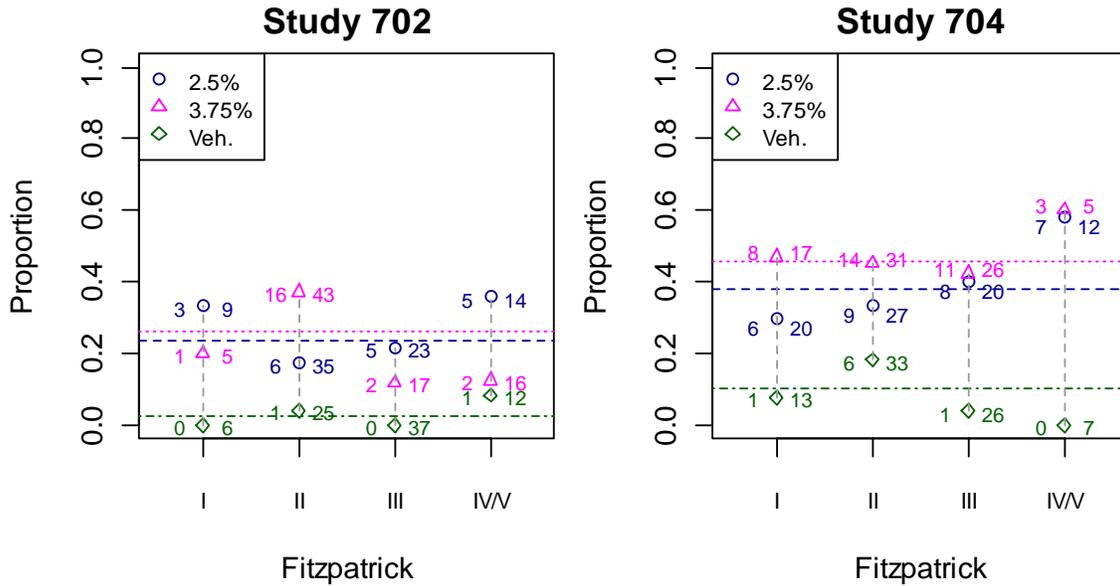


Figure 7 – Complete Clearance Rates by Gender (3-Week Cycle Studies)



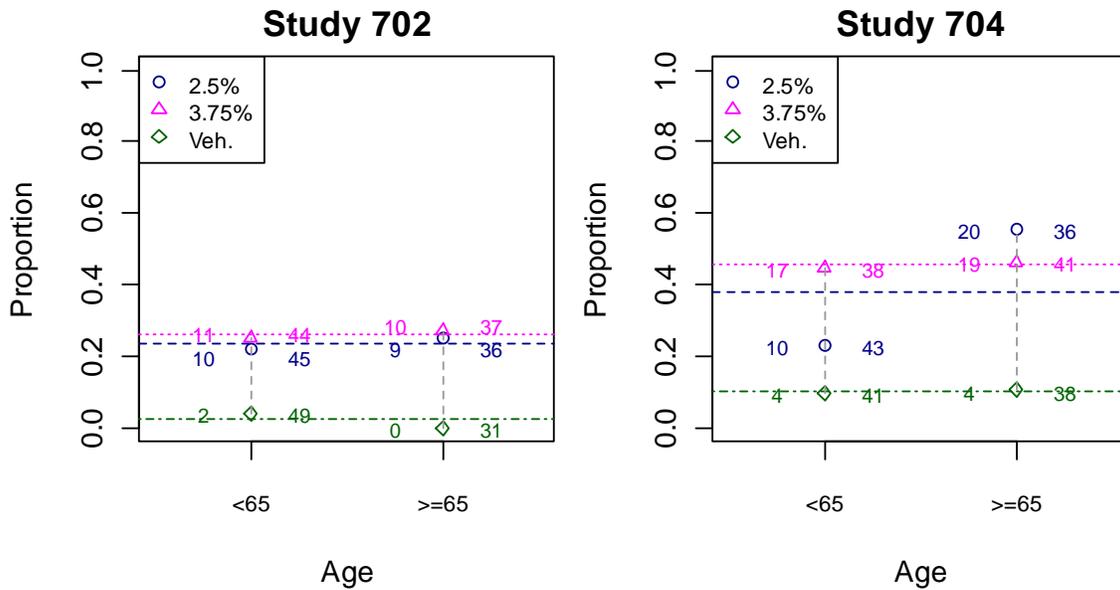
All subjects except for one were classified as white (the remaining subject was American Indian/Alaska Native). About 5% of subjects in Study 0702 and only one subject in Study 0704 were Hispanic. Therefore subgroup analyses by race are not feasible. Instead, the complete clearance rates by Fitzpatrick Skin Type are presented in Figure 8. The Fitzpatrick Skin Type classification does not appear to have any impact on the clearance rates.

Figure 8 – Complete Clearance Rates by Fitzpatrick Skin Type



Age group (<65 vs. ≥ 65) does not appear to have an impact on clearance rates. See Figure 9.

Figure 9 – Complete Clearance Rates by Age Group

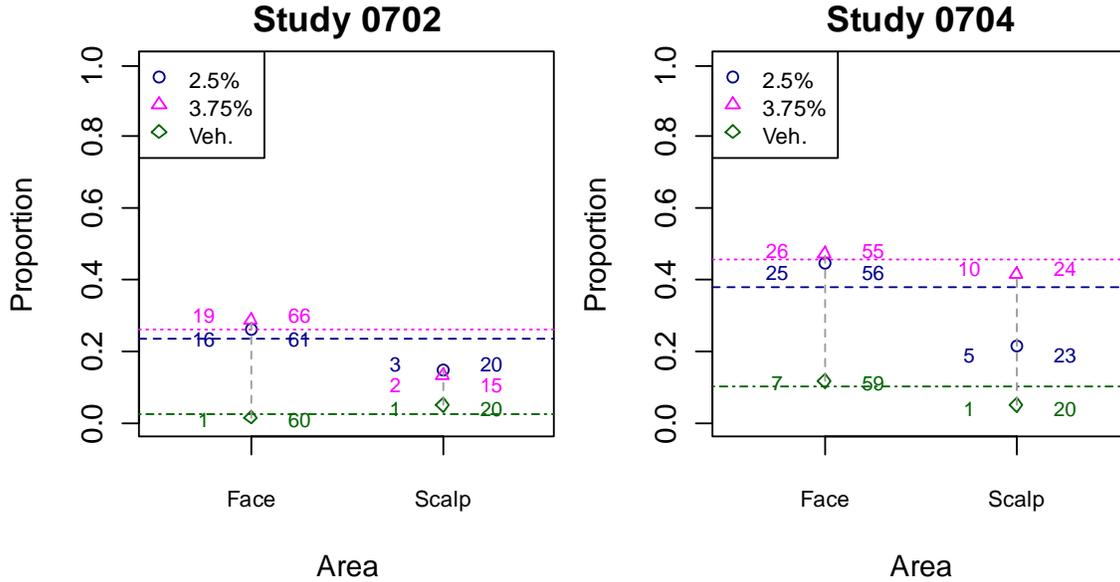


4.2 Other Special/Subgroup Populations

4.2.1 Treatment Region and Baseline Lesions

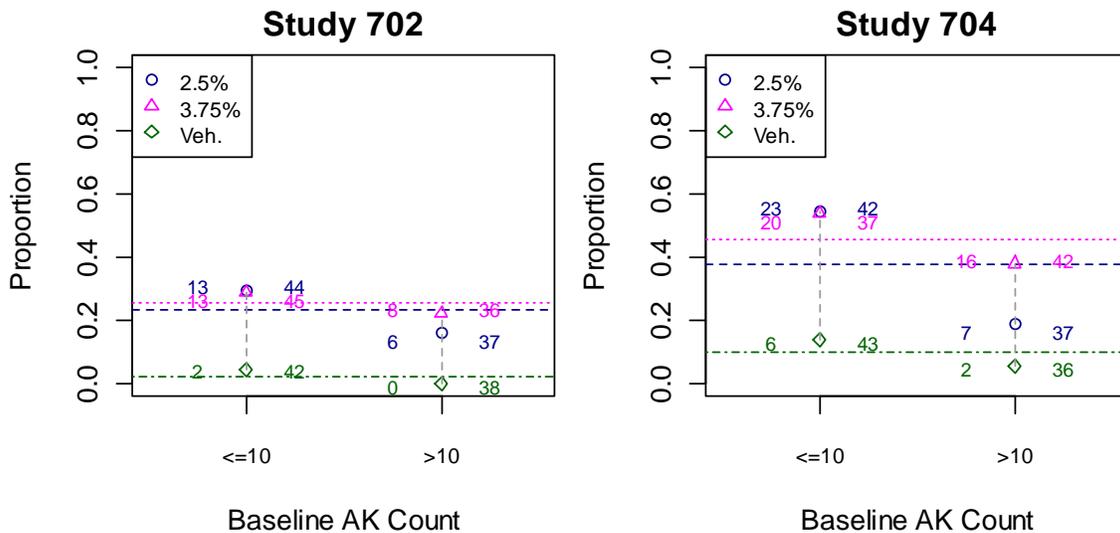
Subjects treated lesions on either the face or scalp, but not both. The location of the treatment area does not appear to have much of an impact on the response rates, though the response rates were slightly higher on the face than the scalp (see Figure 10).

Figure 10 – Complete Clearance Rates by Treatment Region



Subjects who used 3.75% imiquimod had similar clearance rates whether they were enrolled with 5-10 lesions at baseline or more than 10 lesions. However, among subjects who used 2.5% imiquimod, subjects enrolled with 10 or fewer lesions had higher clearance rates than those who had more than 10 lesions. See Figure 11.

Figure 11 – Complete Clearance Rates by Baseline AK Count



4.2.2 Additional Gender Subgroups

As noted in Section 4.1, female subjects had higher clearance rates on 2.5% imiquimod than 3.75% imiquimod in both Studies 0702 and 0704, though the number of female subjects was relatively small. This section includes two additional explorations of factors that could have an influence on gender. As female subjects primarily have treatment

regions on the face, Figure 12 presents the clearance rates by gender and area. However, even when only subjects treating facial regions are compared, the interaction is still present (i.e. males still have higher response on 3.75% while females have higher response on 2.5%). Thus the fact that female subjects had higher clearance rates on 2.5% does not appear to be explained by the fact that female subjects almost exclusively treat the face. Similarly, although female subjects tend to have fewer lesions at baseline (most female subjects had 10 or fewer lesions), both the high and low baseline count groups for females had higher response rates for 2.5% while both groups for males had higher response rates for 3.75% (Figure 13). Thus, it is unclear why the relatively small number of female subjects in both Studies 0702 and 0704 responded better to 2.5% imiquimod than 3.75% imiquimod.

Figure 12 – Complete Clearance Rates by Gender and Treatment Region

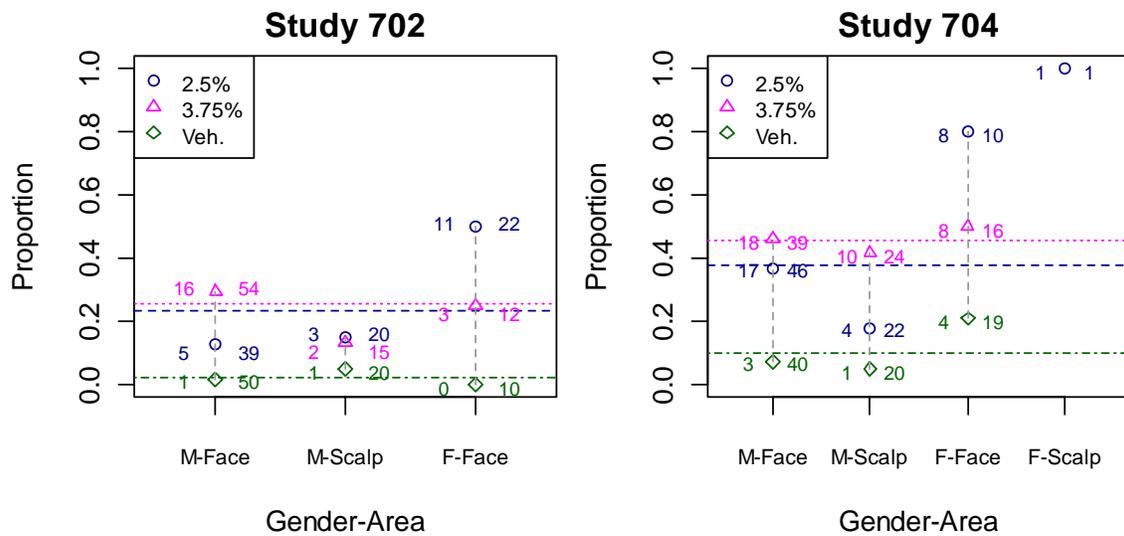
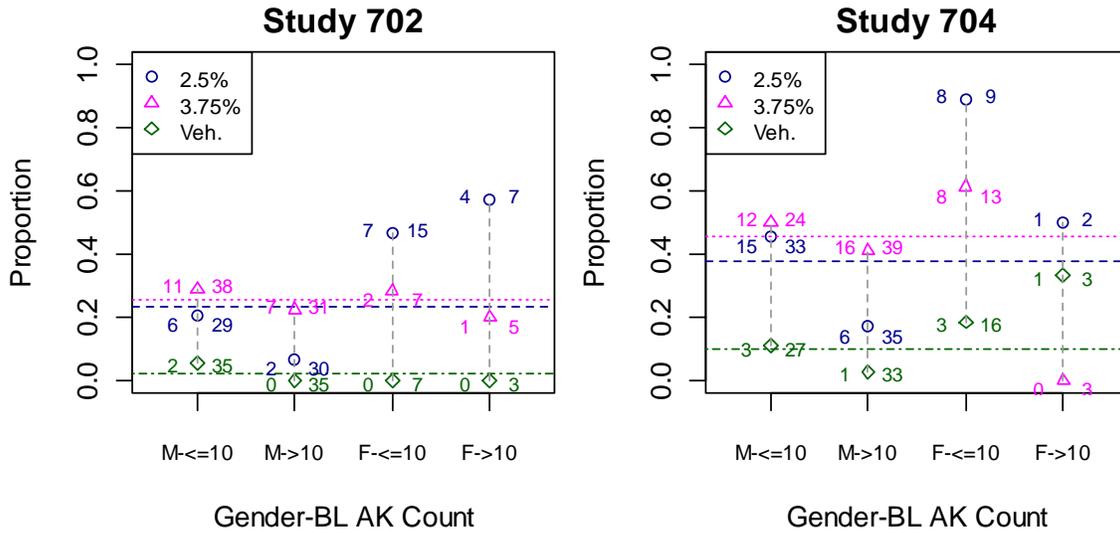


Figure 13 - Complete Clearance Rates by Gender and Baseline AK Count



5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The applicant has demonstrated that imiquimod cream 3.75% applied once daily to the face or scalp in two 2-week cycles is superior to vehicle in the treatment of AK in two studies. The studies also evaluated 2.5% imiquimod cream. The complete clearance rates at Week 14 (8 weeks post-treatment) are presented in Table 25. The 3.75% cream had slightly higher clearance rates than the 2.5% cream in both studies. The 3.75% cream also had slightly higher rates of adverse events than the 2.5% cream (47-49% vs. 43-44%). Subjects who could not tolerate the irritating effects of treatment were permitted to take rest periods. Subjects using the 3.75% cream also had more and longer rest periods than subjects using the 2.5% cream, particularly in the second treatment cycle (9-13% of subjects for an average of 5.3 to 8.2 days vs. 6-8% of subjects for an average of 2.6 to 4.3 days).

Table 25 - Complete Clearance Rates 8 Weeks Post-Treatment

| Study | Imiquimod 2.5% | Imiquimod 3.75% | Vehicle |
|-------|----------------|-----------------|--------------|
| 0702 | 19/81 (23.5%) | 21/81 (25.9%) | 2/80 (2.5%) |
| 0704 | 30/79 (38.0%) | 36/79 (45.6%) | 8/79 (10.1%) |

Note: all p-values versus vehicle were ≤ 0.001 and are significant under Hochberg’s method.

The response rates observed in Study 0704 were somewhat higher than those observed in Study 0702. Exploratory analyses based on baseline or demographic characteristics or treatment compliance did not identify any reasons for the difference. Note that variation in complete clearance rates between studies has also been observed in other development programs for topical AK treatments (for example, in the development programs for imiquimod 5% cream (3 times weekly for 16 weeks; NDA 20-723) (b) (4)

(b) (4) Thus the situation of differential response rates between studies for topical treatment of AKs is not limited to this application.

When clearance rates are analyzed by gender, although the clearance rates for males and females using 3.75% imiquimod were similar, female subjects using 2.5% imiquimod had higher response rates than those using 3.75% imiquimod (and higher than males using 2.5% imiquimod). The number of female subjects was relatively small, however. The higher response rates observed in female subjects using 2.5% imiquimod was not replicated in the 3-week cycle studies, where no gender effect was observed. Because of the relatively small number of female subjects in the studies, it is not clear whether the observed interaction could be generalized to a broader population.

One investigator in Study 0704 had problems with the randomization of 5 out of 15 subjects enrolled at the site. Four of the cases stemmed from the site having insufficient treatment kits on hand for the IVRS to appropriately assign treatment. The investigator issued treatment kits from the stock on hand, rather than wait for additional kits to arrive and then receive the allocation from the IVRS.

As part of the development program, the applicant also conducted two studies with a 3-week cycle regimen. Although the 3-week regimen and the 2-week regimen were not compared within the same studies, the 3-week cycle regimen did not appear to offer efficacy advantages over the 2-week cycle regimen and leads to longer exposure.

5.2 Conclusions and Recommendations

The applicant has demonstrated that imiquimod cream 3.75% applied once daily to the face or scalp in two 2-week cycles is superior to vehicle in the treatment of AK in two studies ($p < 0.001$, significant under Hochberg's method). The studies enrolled subjects with 5 to 20 visible or palpable AKs in an area that exceeded 25 cm² on either the face or balding scalp. The primary efficacy endpoint was complete clearance of lesions in the treatment area 8 weeks post-treatment (Week 14). The studies also demonstrated that imiquimod 2.5% cream was superior to vehicle for the same treatment regimen in two studies ($p < 0.001$, significant under Hochberg's method). The 3.75% cream had slightly higher observed clearance rates than the 2.5% cream. The secondary analyses of the AK lesion counts ($\geq 75\%$ clearance and percent reduction in lesions) also demonstrated statistical significance at Week 14. Lesion counts generally increased during active treatment periods, and usually returned to baseline levels between the two treatment periods.

The local skin reactions of erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration were actively assessed during and after treatment. All of these events increased during active treatment with imiquimod, and returned to baseline levels after treatment.

Signatures/Distribution List

Primary Statistical Reviewer: Kathleen Fritsch, PhD
Date: 8/6/2009

Statistical Team Leader: Mohamed Alosh, PhD

cc:

DDDP/Walker

DDDP/Lindstrom

DDDP/Lolic

DDDP/Turner

OBIO/Patrician

DBIII/Wilson

DBIII/Alosh

DBIII/Fritsch

| Linked Applications | Submission Type/Number | Sponsor Name | Drug Name / Subject |
|---------------------|------------------------|--------------|--------------------------------|
| ----- NDA 22483 | ----- ORIG 1 | ----- | ----- IMIQUIMOD 3.75% CREAM |

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
08/06/2009

MOHAMED A ALOSH
08/06/2009

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA/BLA Number: 22-483 **Applicant:** Graceway
Drug Name: Imiquimod 3.75% **NDA/BLA Type:** 505(b)(1)

Stamp Date: 12/19/08
Indication: Actinic Keratoses

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter for RTF | Yes | No | NA | Comments |
|----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|-----------|-----------------|
| 1A | Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc. | | | X | |
| 1B | Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc. | X | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated. | X | | | |
| 4 | Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets). | X | | | |

THE STATISTICAL SECTION OF THE APPLICATION **IS** FILEABLE

| Content Parameter (possible review concerns for 74-day letter) | Yes | No | NA | Comment |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|-----------|----------------|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | X | | | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | X | | | |

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Requests to the Applicant for the 74-day letter.

Please submit the original treatment assignments (kit numbers) and associated treatment as generated by the IVRS for all subjects in Studies 702, 703, 704, and 705. You have noted that several subjects in Studies 704 and 705 were misrandomized; however, only the information on the kit number actually allocated and associated treatment, not the kit number originally assigned are provided in the listings of Appendix 16.1.7 of the respective study reports. The listings should permit the Agency to verify the misrandomizations described in the study reports. Please also provide information on the information that investigators provided to the IVRS and how the IVRS determined the appropriate kit numbers in Cycle 2 for subjects assigned to incorrect kits in Cycle 1. If possible, please submit the randomization lists as SAS transport files.

Please provide additional information regarding the randomization problems Site 30 in Study 704 experienced, including why the site was unable to receive randomization information from ClinPhone and how the study 'self-randomized' subjects.

The only datasets that contain the randomized treatment codes are the derived analysis datasets (e.g. ad_ops and ad_opv). The applicant should submit a 'source dataset' containing the randomization codes suitable for merging with the other 'CRF source' datasets in Studies 702, 703, 704, and 705.

Reviewing Statistician

Date

Supervisor/Team Leader

Date

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

/s/

Kathleen Fritsch
2/2/2009 09:07:53 AM
BIOMETRICS

Mohamed Alesh
2/2/2009 11:39:22 AM
BIOMETRICS