

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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STATISTICAL REVIEW(S)



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STATISTICAL REVIEW AND EVALUATION
NEW DRUG APPLICATION
CLINICAL STUDIES

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Locoid[®] Lotion, 0.1% has been demonstrated to be statistically superior to vehicle in one pediatric pivotal study (04-103) and one adult supportive study (03-074) in the treatment of atopic dermatitis. Efficacy was evaluated using the success rate based on the Physician Global Assessment (PGA) score at Day 29. Table 18 presents the results of the primary endpoint. The differences in the success rates were statistically significant with p-values of less than 0.0001 in both studies.

Table 1: Efficacy Results - Number (Proportion) of successes on PGA

| Study | Locoid [®] Lotion | Vehicle | p-value* |
|---------------------|----------------------------|----------|----------|
| | N=139 | N=145 | |
| 04-103 (Pivotal) | 68 (49%) | 35 (24%) | <0.0001 |
| 03-074 (Supportive) | 84 (56%) | 49 (33%) | <0.0001 |

* p-value was calculated using CMH test, stratified by pooled sites

Source: MOD 5, VOL 10, pg. 53 and MOD 5, VOL 3, pg. 56

The adverse event rates were higher in vehicle subjects than Locoid[®] subjects. The most common adverse events were application site AEs, which was reported in approximately 8% of the subjects. The next common adverse event was nasopharyngitis.

1.2 Brief Overview of Clinical Studies

The sponsor conducted two Phase 3 studies, one pivotal study (04-103) in the pediatric population and one supportive study (03-074) in the adult population, to evaluate the safety and efficacy of Locoid[®] Lotion, 0.1% versus vehicle in the treatment of atopic dermatitis (AD). A total of 284 and 301 subjects with mild to moderate AD were randomized in a 1:1 ratio to either Locoid[®] or vehicle from Studies 04-103 and 03-074, respectively. Subjects were on treatment for 4 weeks. Efficacy was evaluated on Day 29 using the success rate based on the PGA score. All study centers were in the United States.

1.3 Statistical Issues and Findings

The sponsor submitted the results of one pivotal study (04-103) conducted in the pediatric population and one supportive study (03-074) in the adult population to support the efficacy and safety claim for Locoid[®] Lotion, 0.1% in the treatment of atopic dermatitis. The sponsor

conducted the pivotal study under the protocol that was agreed upon with the Agency in terms of study design and the primary endpoint. Efficacy was evaluated on Day 29 using the proportion of successes based on the PGA score. The difference in the success rates were statistically significant with a p-value of less than 0.0001 in the Pivotal study. The efficacy result were relatively consistent across subgroups and investigative sites. The protocol defined change from baseline in pruritus at Day 29 as the secondary endpoint which was also statistically significant with a p-value less than 0.0001.

The supportive study results were consistent with the findings from the pivotal study. The difference in the success rates were statistically significantly with a p-value of less than 0.0001.

2 INTRODUCTION

2.1 Overview

The active treatment of this study is hydrocortisone butyrate (HCB), a synthetic, non-fluorinated, glucocorticoid developed in the 1970's, known by the brand name Locoid[®]. Locoid[®] was approved for marketing in the United States in the following four topical formulations.

| | | |
|------------------|------------|-------------------|
| Locoid Cream | NDA 18-514 | March 3, 1982 |
| Locoid Ointment | NDA 18-652 | October 29, 1982 |
| Locoid Solution | NDA 19-116 | February 25, 1997 |
| Locoid Lipocream | NDA 20-769 | September 8, 1997 |

In the current application of Locoid[®] Lotion, 0.1%, the sponsor is seeking an indication of mild to moderate atopic dermatitis (AD) in patients from 3 months and older, applied twice daily for up to four weeks.

The sponsor initially proposed study protocol 03-074, an adult AD trial. At the guidance meeting dated January 20, 2004, the Agency informed the sponsor that this study could be only supportive as AD is primarily seen in the pediatric population. It was noted that the enrollment had already started at the time this meeting was held. The sponsor proposed study protocol 04-103, a pediatric AD trial, which was discussed in an End-of-Phase (EOP) 2 meeting held March 29, 2004. At this meeting the sponsor understood that Study 03-074 may only be supportive and the Agency agreed that the proposed study (04-103) may be adequate as the sole Phase 3 pivotal trial for this line extension product, provided the efficacy results are robust and persuasive. The sponsor submitted a single Phase 3 study as SPA (stamp date June 10, 2004). Through the meetings and SPA review, the sponsor and Agency come to an agreement on the key aspects of the study design and endpoints. Table 2 lists the Phase 3 clinical study programs. This review evaluates the efficacy and safety of Study 04-103 as the pivotal study and includes a brief description of the supportive study (03-074) and its efficacy results in Section 3.2.

Table 2: Overview of Phase 3 Clinical Studies

| Study | Population | Study Period | Number of Subjects | | |
|------------------------|------------|------------------|----------------------------|---------|-------|
| | | | Locoid [®] Lotion | Vehicle | Total |
| 04-103 (Pivotal) | Pediatric | 10/19/04–9/20/05 | 139 | 145 | 284 |
| 03-074 (Supportive) | Adult | 8/19/03–3/24/04 | 151 | 150 | 301 |

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 as a paper CTD format. The datasets used in this review are archived at \\Cdsub1\n22076\N_000\2006-09-12\04-103 and \\Cdsub1\n22076\N_000\2006-09-12\03-074.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

The sponsor conducted one pivotal Phase 3 study (04-103) in the pediatric population and one supportive Phase 3 study (03-074) in the adult population to evaluate the safety and efficacy of Locoid[®] Lotion, 0.1% in the treatment of mild and moderate AD. Protocol 04-103 was evaluated as a SPA in June 2004. This study was a multicenter, double-blind, vehicle-controlled, and randomized study, which planned to enroll 280 subjects from 14 investigational sites. The actual enrollment was 284 subjects from 15 sites. The inclusion criteria included male or female subjects, who were 3 months to less than 18 years of age with mild to moderate AD (Physician's Global Assessment (PGA) score of 2 or 3) and a minimum of 10% body surface area (%BSA) involvement.

The enrolled subjects were randomly assigned in a 1:1 ratio to either Locoid[®] or vehicle. The randomization resulted in 139 and 145 subjects for Locoid[®] and vehicle, respectively. The subjects' caregivers were instructed to apply the treatment or vehicle to the affected area twice daily for 4 weeks. If the subject achieved total clearing (PGA score of 0) at the Day 22 evaluation, treatment was discontinued at that time. Clinical evaluations were conducted at baseline, Days 8, 22, and 29. Regardless of the duration of treatment, all subjects were required

to return for the final assessment on Day 29, which was the primary time for efficacy assessment. For efficacy evaluation, the following endpoints were specified in the protocol.

- Primary: Percentage of subjects who achieved success at Day 29.
Success was defined as subjects with PGA score of 0 or 1 that had at least a two point reduction from baseline.
- Secondary: Change from baseline in pruritus at Day 29.

PGA and pruritus scores were defined as the following.

PGA:

- 0 Clear: No signs of inflammatory AD
- 1 Almost Clear: Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present
- 2 Mild: Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild
- 3 Moderate: Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate
- 4 Severe: Deep/dark red erythema, and marked and extensive elevation; excoriation and oozing/crusting are present.

Pruritus:

- 0 None: None
- 1 Mild: Occasional, slight itching/scratching
- 2 Moderate: Constant or intermittent itching/scratching/discomfort which is not disturbing sleep
- 3 Severe: Bothersome itching/scratching/discomfort which is disturbing sleep.

The protocol and submission defined the intent-to-treat (ITT) population as all subjects enrolled in the study and dispensed study medication. Subjects were eligible for the per protocol (PP) analysis if (i) they did not take or apply any interfering concomitant medications; (ii) they completed the final visit (Day 29 \pm 3 days) and missed no more than one Interim Visit with the exception of discontinuation due to adverse event related to study treatment or treatment failure; (iii) they did not miss more than 4 consecutive doses and applied at least 75% but no greater than 125% of the expected doses. The ITT and PP populations were analyzed for safety and efficacy, where ITT analysis was the primary.

The analysis methods proposed in the protocol and the submission were the following:

- The primary endpoint, success rate, was analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified by investigational centers. The center by treatment interaction was tested using the Breslow-Day test at a significant level of 0.10.
- Change from baseline in pruritus at Day 29 was also analyzed with the CMH test stratified by analysis centers.
- Last observation carried forward (LOCF) was used to impute missing values in the efficacy endpoints. In addition to LOCF, two sensitivity analyses were conducted: one analysis

imputed all missing data as failures, and the second analysis imputed all missing data as successes.

- The target number of subjects per treatment arm per site was at least 8. Sites with smaller enrollment were combined by taking the site with the smallest enrollment and combining it with the largest site that did not meet the minimum of 8 subjects per treatment arm. If further combination was needed, the site with the second smallest enrollment was combined with the site with the second largest enrollment.

Study sites were pooled into 11 analysis groups, which were used in the efficacy analyses. Table 3 presents the pooled sites and the number of subjects in each site before pooling.

Table 3: Enrollment by pooled sites (04-103)

| Pooled Site | Original Site | Number of Subjects | Pooled Site | Original Site | Number of Subjects |
|-------------|---------------|--------------------|-------------|---------------|--------------------|
| 1 | 1, 3 | 15, 2 | 7 | 9 | 27 |
| 2 | 2, 4, 12 | 14, 3, 5 | 8 | 10 | 32 |
| 3 | 5, 15 | 7, 14 | 9 | 11 | 22 |
| 4 | 6 | 23 | 10 | 13 | 30 |
| 5 | 7 | 29 | 11 | 14 | 29 |
| 6 | 8 | 32 | | | |

Source: Reviewer analysis

3.1.2 Subject Disposition

The study enrolled a total of 284 subjects from 15 study sites and randomized them in a 1:1 ratio to treatment and vehicle arms. Thus, 139 subjects were randomized to Locoid[®] and 145 to the vehicle arm. Table 4 presents the reasons for study discontinuation.

The number of subjects who discontinued the study was higher in the vehicle arm than the Locoid[®] arm, at 7 (5%) and 25 (17%) for Locoid[®] and vehicle arms, respectively. The most common reason for study discontinuation in the Locoid[®] arm was lost to follow-up. For the vehicle arm, subject request (7 subjects) and lack of efficacy (6 subjects) were the most common reasons for discontinuation. The two subjects included in 'Other' discontinued the study due to the subject being removed from the care of her mother by social service and the subjects parent withdrawing consent due to family problems.

Table 4: Reason for Study Discontinuation

| | Locoid [®] Lotion N=139 | Vehicle N=145 |
|----------------------------------|-------------------------------------|------------------|
| Subjects who discontinued | 7 (5%) | 25 (17%) |
| <i>Reason</i> | | |
| Subject Request | 2 (1%) | 7 (5%) |
| Lost to Follow-up | 5 (4%) | 5 (3%) |
| Lack of Efficacy | 0 (0%) | 6 (4%) |
| Adverse Event | 0 (0%) | 5 (3%) |
| Other | 0 (0%) | 2 (1%) |

Source: MOD 5, VOL 10, pg. 48 and reviewer analysis

3.1.3 Baseline and Demographic Data

Table 5 presents the baseline demographic data. The baseline demographic variables were generally balanced across treatment arms. The mean age of the subjects was approximately 7.1 years and the age range was from 3 months to 17.8 years. Locoid[®] had a higher proportion of female subjects (54%) than males, whereas the vehicle arm had a higher proportion of male subjects (54%) than females. Ten subjects (4 in Locoid[®] arm and 6 in the vehicle arm) reported multiple races. More than 60% of the subjects were White. Race was relatively balanced across treatment arms.

Table 6 presents the baseline PGA scores and the extent of atopic dermatitis (%BSA) at baseline. The baseline severity scores, the PGA score and body surface area (%BSA), were fairly balanced between the two arms. Locoid[®] had a marginally higher proportion of subjects with moderate severity (PGA score: 3) and a slightly higher mean %BSA than the vehicle at baseline. Although the study population was mild to moderate AD (PGA score: 2 or 3), one subject with baseline PGA score of 4 was enrolled in the vehicle arm. All subjects had AD on at least 10% of their body surface. The median %BSA was 19.5% and 20.3%, and the maximum surface area was 95% and 88.5% for Locoid[®] and vehicle arms, respectively.

Table 5: Baseline Demographic Data

| | Locoid [®] Lotion N=139 | Vehicle N=145 |
|----------------------------------|-------------------------------------|------------------|
| Age (in years) | | |
| mean (std) | 7.3 (5.3) | 7.0 (5.1) |
| median | 6.5 | 6.4 |
| min,max | (0.3,17.8) | (0.4,17.6) |
| Gender | | |
| Male | 64 (46%) | 79 (54%) |
| Female | 75 (54%) | 66 (46%) |
| Race[†] | | |
| White | 92 (66%) | 93 (64%) |
| Black/African American | 40 (29%) | 52 (36%) |
| Asian | 9 (6%) | 4 (3%) |
| Native Hawaiian/Pacific Islander | 0 (0%) | 2 (1%) |
| American Indian/Alaska Native | 2 (1%) | 2 (1%) |

[†] Subjects could report multiple race categories.

Source: MOD 5, VOL 10, pg. 74

Table 6: Baseline Severity

| | Locoid [®] Lotion N=139 | Vehicle N=145 |
|--|-------------------------------------|------------------|
| Physician's Global Assessment Score | | |
| Mild (2) | 65 (47%) | 69 (48%) |
| Moderate (3) | 74 (53%) | 75 (52%) |
| Severe (4) | 0 (0%) | 1 (1%) |
| Extent of Atopic Dermatitis (%BSA) | | |
| Mean (std) | 26.4 (18.5) | 25.6 (17.2) |
| Median | 19.5 | 20.3 |
| Min, Max | (10,95.0) | (10,88.5) |

Source: MOD 5, VOL 10, pg.84

3.1.4 Primary Efficacy Endpoint

3.1.4.1 ITT Analyses

The protocol defined success as subjects who reached PGA score of 0 or 1 at Day 29, that had at least a two point reduction from baseline. (Subjects who had a PGA score of 2 at baseline must

have achieved 0 (Clear) at Day 29 to be considered as success.) Table 7 presents the sponsor's primary efficacy results in the intent-to-treat (ITT) population, which was confirmed by this reviewer. At Day 29, the primary time point, 49% of the Locoid® subjects reached success status while 24% of the vehicle arm subjects were successes. The difference of the success rates in the two arms was highly statistically significant with a p-value of <0.0001, establishing the efficacy of Locoid® at Day 29.

Table 7: Primary Efficacy Endpoint Results (ITT)

| | Locoid® Lotion N=139 | Vehicle N=145 | p-value * |
|-------------------------|-------------------------|------------------|-----------|
| Number (%) of Successes | 68 (49%) | 35 (24%) | <0.0001 |

* p-value was calculated using CMH test, stratified by pooled sites

Source: MOD 5, VOL 10, pg. 53

3.1.4.2 Sensitivity Analysis of the Primary Efficacy Endpoint

Per protocol, last observation carried forward (LOCF) was used to impute missing data in the analysis of the previous section. The details of the numbers and proportions of missing observations in each treatment arm over time is provided in Appendix A.1. The sponsor conducted two sensitivity analyses to ensure that the efficacy results were not driven by the imputation method. The first analysis imputed all missing observations as successes for both arms and the second analysis imputed missing data as failures. Table 8 presents primary efficacy results using these imputation methods.

Table 8: Sensitivity Analyses on Primary Endpoint

| | Locoid® Lotion N=139 | Vehicle N=145 | p-value * |
|----------------------|-------------------------|------------------|-----------|
| Imputed Subjects | 7 (5%) | 25 (17%) | |
| Success [†] | 67 (48%) | 35 (24%) | < 0.0001 |
| Success [‡] | 74 (53%) | 60 (41%) | 0.0409 |

* p-values are calculated using CMH statistic stratified by pooled sites

[†] Missing data imputed as failures

[‡] Missing data imputed as successes

Source: MOD 5, VOL 10, pg. 59 and reviewer analysis

The total number of missing subjects at Day 29 was 32 observations (11.3%), 7 (5%) and 25 (17%) in Locoid[®] and vehicle arms, respectively. Thus the vehicle arm had a larger number of drop-outs than the Locoid[®] arm. Imputing the missing data as successes is a conservative approach, since the vehicle arm had more missing data and the most common reasons for drop-out were subject request and lack of efficacy, while that of Locoid[®] was lost to follow-up. However, even using this approach, the difference in the success rates of the two arms was statistically significant with a p-value of 0.0409, in favor of the treatment arm. The second analysis (imputing missing data as failures) results were similar to that using LOCF. The sensitivity analysis ensures that the statistically significant result was not driven by using LOCF as the imputation method.

3.1.4.3 Per Protocol Analysis

The per protocol (PP) population excluded subjects who (i) took or applied any interfering concomitant medications; (ii) did not complete the final visit (Day 29 \pm 3 days) and missed more than one interim visit with the exception of discontinuation due to adverse event related to study treatment or treatment failure; (iii) missed more than 4 consecutive doses or applied less than 75% or greater than 125% of the expected doses. A total of 75 subjects (26%) were excluded from the PP population, 35 (25.2%) and 40 (27.6%) subjects in the Locoid[®] and vehicle arms, respectively. The most common reason for exclusion in the vehicle arm was non-dosing compliant (21 subjects) followed by prohibited medication (16 subjects). For the Locoid[®] arm, the most common reasons for exclusion were the same as that in the vehicle arm in reverse order, prohibited medication (18 subjects) and non-dosing compliant (13 subjects). Note that some subjects were excluded for multiple reasons. Table 9 presents the results of the primary endpoint analysis at Day 29 based on the per protocol population.

Table 9: Primary Efficacy Endpoint Results (PP)

| | Locoid [®] Lotion | Vehicle | p-value * |
|-----------------------|----------------------------|----------|-----------|
| | N=104 | N=105 | |
| Number (%) of Success | 53 (51%) | 25 (24%) | <0.0001 |

* p-value was calculated using CMH test, stratified by pooled sites

Source: MOD 5, VOL 10, pg. 53

The proportion of successes in the PP population was slightly higher than that of the ITT population in the Locoid[®] arm at 51%. However, the PP population success rate in the vehicle arm was the same as that of the ITT population at 24%. The difference in the proportion of successes of the two arms was statistically significant with a p-value less than 0.0001. The ITT

and PP population primary endpoint analyses results were similar, which further supports the superiority of Locoid[®] over vehicle.

3.1.5 Secondary Efficacy Endpoint

The secondary endpoint defined in the protocol was change from baseline in pruritus score at Day 29. The sponsor proposed to analyze the secondary endpoint with Cochran-Mantel-Haenszel (CMH) test, stratified by analysis centers. However, the sponsor analyzed the secondary endpoint using an analysis of variance (ANOVA) model with treatment and analysis centers as factors. This reviewer analyzed the secondary endpoint according to the method proposed in the protocol. Due to small cells, CMH was applied without stratification by analysis center. Table 10 presents the results of the secondary endpoint analysis.

Table 10: Change from baseline in pruritus score at Day 29 (ITT)

| Change from baseline | Locoid [®] Lotion | Vehicle | p-value* |
|----------------------|----------------------------|----------|----------|
| | N=139 | N=145 | |
| -2 | 1 (<1%) | 1 (<1%) | <0.0001 |
| -1 | 1 (<1%) | 12 (8%) | |
| 0 | 25 (18%) | 50 (34%) | |
| 1 | 43 (31%) | 48 (33%) | |
| 2 | 56 (40%) | 29 (20%) | |
| 3 | 13 (9%) | 5 (3%) | |

* p-value was calculated using CMH test

Source: Reviewer analysis

Forty percent of Locoid[®] had a 2 grade decrease in pruritus score at Day 29 from baseline. Whereas the majority of the vehicle arm subjects experienced no change (34%) or 1 grade decrease (33%). Also, 12 subjects (8%), in the vehicle arm, pruritus score increased from baseline at Day 29. The two arms' change from baseline in pruritus score at Day 29 was statistically significant with a p-value less than 0.0001.

Table 11 presents the mean (standard deviation) change from baseline in pruritus score at Day 29 along with the p-value obtained from using an ANOVA model. Treatment, analysis centers, and treatment by center interaction term were included in the model as factors.

Table 11: Change from baseline in pruritus score at Day 29 using ANOVA

| | Locoid [®] Lotion | Vehicle | p-value * |
|-----------|----------------------------|-------------|-----------|
| | N=139 | N=145 | |
| Mean (SD) | 1.37 (0.96) | 0.74 (1.01) | <0.0001 |

* p-value was ANOVA with treatment, analysis centers, and treatment by analysis center interaction term as factors.

Source: Reviewer analysis

The mean (sd) change in pruritus score at Day 29 from baseline was 1.37 (sd 0.96) in Locoid[®] and 0.74 (sd 1.01) in the vehicle arm. The difference in the mean change in pruritus score of the two arms was statistically significant with a p-value of less than 0.0001. The sponsor's ANOVA model did not include the treatment by analysis center interaction term. The results of the sponsor's analysis agreed with the reviewer's result with a p-value less than 0.0001.

It should be noted that pruritus was a secondary endpoint only in the pediatric study (04-103). In the adult study (03-074), pruritus was studied as an 'other' endpoint without any statistical testing conducted.

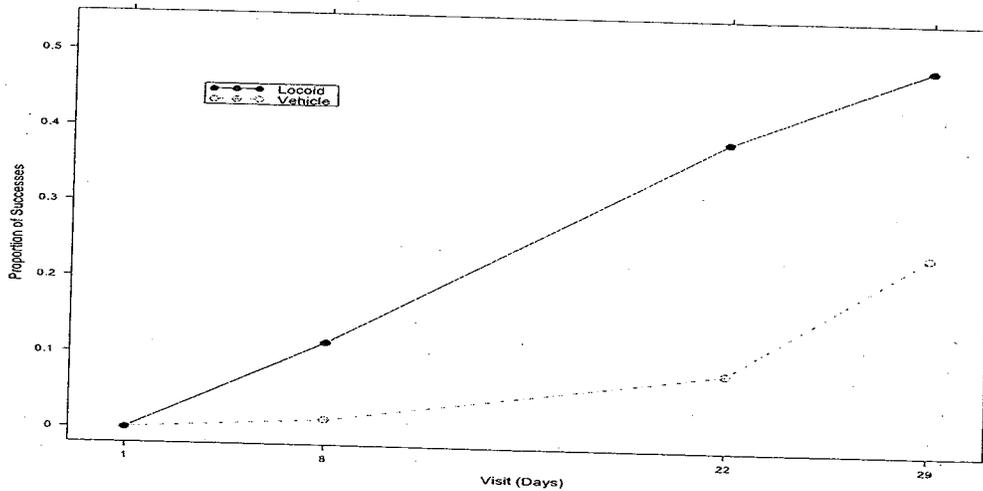
3.1.6 Efficacy Results over Time

Subjects were followed for a total of 29 days, and were evaluated at baseline, Days 8, 22, and 29. Figure 1 presents the primary endpoint success rate over time.

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Figure 1: Efficacy Results over Time



The success rate in the Locoid[®] arm was marginally higher than that of the vehicle arm at Day 8. The difference in success rates is largest at Day 22. Both arms' success rate continued to increase throughout the treatment period, however the vehicle arm at a much smaller degree.

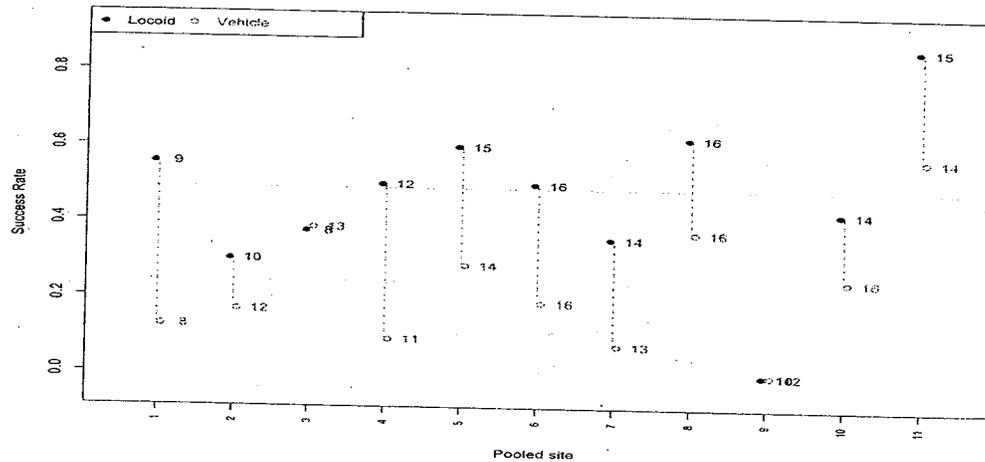
3.1.7 Efficacy Results by Center

This study involved 15 investigators, all from the United States. Each investigator enrolled between 2 to 32 subjects. Sites with smaller enrollment were combined by taking the site with the smallest enrollment and combining it with the largest site that enrollment was less than the target, 8 subjects per arm. There were 11 pooled investigative sites.

Figure 2 presents the treatment success rate and the number of subjects enrolled in each pooled site by treatment. The success rate of both arms appeared to be relatively consistent across pooled sites, and therefore the results do not seem to be driven by extreme sites. The Breslow-Day test results also supported this conclusion with a p-value of 0.8740.

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Figure 2: Efficacy by Pooled Sites



3.2 Efficacy Results from Supportive Study (03-074)

As indicated in Section 2.1, the sponsor agreed with the Agency, at the End of Phase (EoP) 2 meeting dated 3/29/04, that Study 03-074 would be considered as a supportive study. Efficacy was measured using a 7-point PGA defined as the following:

- | | |
|---------------------|--|
| 0 Clear: | No inflammatory signs of AD |
| 1 Just Perceptible: | Just perceptible erythema, and just perceptible infiltration/papulation |
| 2 Mild: | Mild erythema, and mild papulation/infiltration |
| 3 Moderate: | Moderate erythema, and moderate papulation/infiltration |
| 4 Marked: | More pronounced erythema, and more pronounced papulation/infiltration |
| 5 Severe: | Severe erythema, and severe papulation/infiltration |
| 6 Extreme: | Severe erythema, and severe papulation/infiltration with oozing/crusting |

The duration of treatment was 21 - 28 days according to the following plan:

- At the Day 14 visit, if PGA score does not equal 0 ($PGA \neq 0$), continue treatment for two more weeks and return for the Day 21 visit for clinical evaluation and at Day 28 for clinical evaluation and Final Visit.
- At the Day 14 visit, if PGA score equals 0, ($PGA = 0$) dose for one more week and return on Day 21 for clinical evaluation.
 - At the Day 21 Visit, if subjects is still clear ($PGA = 0$), then this visit will be considered the Final Visit and activities scheduled for the Final Visit will be conducted.

- At the Day 21 Visit, if subject does not remain clear (PGA \neq 0), then the subject will dose for one more week and return on Day 28 for clinical evaluation and the Final Visit will be conducted.

The sponsor defined treatment success as a PGA score of 0 (cleared) or 1 (just perceptible) at Day 28 and considered subjects without a Day 28 evaluation as failures, unless the subject had PGA scores of 0 at Days 14 and 21. Table 12 presents the primary efficacy results based on the sponsor's definition of treatment success, which was confirmed by this reviewer.

Table 12: Primary Efficacy Endpoint Results using Sponsor's Definition of Success (03-074)

| | Locoid [®] Lotion N=151 | Vehicle N=150 | p-value* |
|----------------------|-------------------------------------|------------------|----------|
| Success [†] | 84 (56%) | 49 (33%) | <0.0001 |

[†] Subjects were dichotomized as "Successes" if a PGA score of 0 (clear) or 1 (just perceptible) on a 7-grade scale at Day 28 was reached, or if cleared (0) on Day 21 and Day 14. Subjects who discontinued the study prior to Day 28 without confirmed clear on Days 14 and 21 were considered "Failures".

* p-value was calculated using CMH test, stratified by pooled sites

Source: MOD 5, VOL 3, pg. 56

Using the sponsor's definition of success, 56% of the Locoid[®] subjects reached success status at Day 28, while 33% of the vehicle arm subjects were successes. The difference of the success rates in the two arms was statistically significant with a p-value of <0.0001, establishing the efficacy of Locoid[®] over vehicle in the adult population.

The sponsor included a sensitivity analysis that defines treatment success as that in the pivotal study, in other words, subjects must have had at least a 2 grade improvement from baseline to be considered successes. This sensitivity analysis used LOCF to impute missing observations at Day 28. This reviewer included two additional sensitivity analyses, using 2 grade improvement from baseline as a criterion for success. The first analysis imputed missing observations at Day 28 as failures unless the subject was confirmed clear (PGA score: 0) on Days 14 and 21, in such case the observation was considered success, per study design. The second sensitivity analysis imputed all missing observations at Day 28, similarly to the completers by generating binomial numbers. Thirty three and 37 observations were imputed in Locoid[®] and vehicle arms, respectively. It should be noted that 18 subjects in Locoid[®] were missing due to being clear at Days 14 and 21, compared to 3 in the vehicle arm. Table 13 presents the sponsor's and reviewer's sensitivity analyses.

Table 13: Sensitivity Analyses on Primary Endpoint (03-074)

| | Locoid [®] Lotion N=151 | Vehicle N=150 | p-value* |
|------------------------|-------------------------------------|------------------|----------|
| Imputed Subjects | 33 (22%) | 37 (25%) | |
| Success ^{§†} | 78 (52%) | 40 (27%) | < 0.0001 |
| Success ^{§‡} | 74 (49%) | 37 (25%) | < 0.0001 |
| Success ^{§‡‡} | 72 (47%) | 37 (25%) | < 0.0001 |

* p-values are calculated using CMH statistic stratified by pooled sites

† Missing data imputed using LOCF.

‡ Missing data imputed as failures, unless subject had PGA score of 0 at Days 14 and 21.

‡‡ Missing data imputed using random binomial numbers.

§ Success was defined as PGA score of 0 or 1 at Day 28, with at least a 2 grade decrease from baseline.

Source: MOD 5, VOL 3, pg. 62 and reviewer analysis

The differences of the success rates in the treatment arms were statistically significant in all three sensitivity analyses with p-values less than 0.0001. These results support the superiority of Locoid[®] over vehicle even when success is defined as PGA score of 0 or 1 at Day 28 with at least a 2 grade decrease from baseline. The treatment success rate and number of subjects enrolled in each pooled site by treatment is provided in Appendix A.2.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The subjects' caregivers were instructed to apply the treatment or vehicle to the affected area twice daily for 4 weeks. Therefore, the expected number of applications was 56. Subjects who were clear at Day 22 (PGA score: 0) discontinued dosing, and consequently their expected number of applications was 42. The mean number of treatment applications in the two arms were similar at 51.4 (range 13-84) and 49.2 (range 2-98), in Locoid[®] and vehicle arms, respectively.

3.3.2 Adverse Events

A total of 104 (37%) subjects reported at least one adverse event (AE). The proportion of subjects who experienced such AE was higher in the vehicle arm than the Locoid[®] arm: 35% and 39% of Locoid[®] and vehicle arms, respectively. Also, the number of AEs reported was higher in the vehicle (85) arm compared to the Locoid[®] arm (69). Table 14 presents the rates

for events that occurred in at least 3% of subjects per treatment arm.

Table 14: Adverse Events that Occured in at Least 3% of Subjects

| Preferred Term | Locoid Lotion | Vehicle | Total |
|--|---------------|----------|-----------|
| | N=139 | N=145 | N= 284 |
| Subjects with an adverse experience | 48 (35%) | 56 (39%) | 104 (37%) |
| Nasopharyngitis | 7 (5%) | 9 (6%) | 16 (6%) |
| Upper respiratory tract infection | 6 (4%) | 4 (3%) | 10 (4%) |
| Ear infection | 4 (3%) | 1 (1%) | 5 (2%) |
| Cough | 3 (2%) | 4 (3%) | 7 (2%) |
| Pyrexia | 5 (4%) | 7 (5%) | 12 (4%) |
| Application site AEs | 2 (1%) | 20 (14%) | 22 (8%) |

Source: MOD 5, VOL 10, pg. 134-136

The most common adverse event was application site AE, which occurred in approximately 8% of the subjects. This adverse event occurred at a much higher rate in the vehicle arm at 14% compared to 1% of the Locoid[®] arm subjects. The next common adverse event was nasopharyngitis (5% of Locoid[®] and 6% of vehicle subjects). There was one serious adverse event occurred to a 1.47 year old male subject on the vehicle arm. This subject was treated for application site eczema. The sponsor stated that this serious adverse event was considered moderate and the relationship to study medication as unassessable.

3.3.3 Application Site Adverse Events

The vehicle arm had a higher rate of subjects who had adverse events concerning application site, 2 (1%) and 20 (14%) in Locoid[®] and vehicle arms, respectively. Table 15 presents the frequency of application site AEs.

The most common adverse event concerning application site was application site burning. A larger proportion of subjects on the vehicle arm (6%) experienced this event than the Locoid[®] arm (1%). In all application site AEs, the vehicle arm experienced local adverse events than Locoid[®] subjects.

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Table 15: Application Site Adverse Events

| | Locoid Lotion N=139 | Vehicle N=145 | Total N= 284 |
|-----------------------------|------------------------|------------------|-----------------|
| Application site AEs | 2 (1%) | 20 (14%) | 22 (8%) |
| <i>Conditions</i> | | | |
| Burning | 1 (1%) | 8 (6%) | 9 (3%) |
| Pruritus | 1 (1%) | 5 (3%) | 6 (2%) |
| Dermatitis | 0 (0%) | 2 (1%) | 2 (1%) |
| Erythema | 0 (0%) | 2 (1%) | 2 (1%) |
| Eczema | 0 (0%) | 1 (1%) | 1 (<1%) |
| Inflammation | 0 (0%) | 1 (1%) | 1 (<1%) |
| Irritation | 0 (0%) | 1 (1%) | 1 (<1%) |

Source: MOD 5, VOL 10, pg. 134

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Table 16 presents the success rates by gender, race, and age groups based on the ITT population. Male subjects had a higher success rate in the treatment arm than the female group. Success rates were relatively consistent across race. With the exception of one subgroup (Age 12 - 18 years), the success rates of Locoid[®] were higher than that of the vehicle arm. In the age 12 years to 18 years group, the success rate in the Locoid[®] arm was slightly lower than that of the vehicle arm. It should be noted that the difference in the number of successes of each arm in the last age group is one subject and that the study was not powered to draw statistical conclusions about subgroups.

Plots of the success rates and their unadjusted 95% confidence intervals by gender (Figure 5), race (Figure 6), and age groups (Figure 7) are presented in Appendix A.3.

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Table 16: Efficacy Results (Number (%) of Successes) by Gender Age and Race

| | | | Locoid [®] Lotion N=139 | Vehicle N=145 |
|--------|------------------|-------------|-------------------------------------|------------------|
| Gender | Male | Total | 64 | 79 |
| | | Success (%) | 37 (58%) | 21 (27%) |
| | Female | Total | 75 | 66 |
| | | Success (%) | 31 (41%) | 14 (21%) |
| Race | White | Total | 88 | 87 |
| | | Success (%) | 46 (52%) | 22 (25%) |
| | Black | Total | 40 | 51 |
| | | Success (%) | 17 (43%) | 12 (24%) |
| | Asian | Total | 9 | 3 |
| | | Success (%) | 5 (56%) | 0 (0%) |
| | Pacific Islander | Total | 0 | 2 |
| | | Success (%) | 0 (0%) | 1 (50%) |
| | American Indian | Total | 2 | 2 |
| | | Success (%) | 0 (0%) | 0 (0%) |
| Age | 3mths - <2yrs | Total | 32 | 29 |
| | | Success (%) | 19 (59%) | 5 (17%) |
| | 2yrs - <6yrs | Total | 32 | 40 |
| | | Success (%) | 16 (50%) | 9 (23%) |
| | 6yrs - <12yrs | Total | 38 | 47 |
| | | Success (%) | 24 (63%) | 13 (28%) |
| | 12yrs - <18yrs | Total | 37 | 29 |
| | | Success (%) | 9 (24%) | 8 (28%) |

Source: MOD 5, VOL 10, pg. 127

4.2 Other Special/Subgroup Populations

The proportion of success rates was explored by baseline disease severity. The sponsor analyzed success rate at Day 29 by baseline PGA score. This reviewer included an additional analysis of success rate by the extent of atopic dermatitis (%BSA) at baseline. The subjects were categorized into two groups, %BSA \leq 20 or %BSA $>$ 20, where 20 was the median %BSA of all subjects. Table 17 presents the success rate by baseline severity.

Success rates were higher for subjects with moderate atopic dermatitis (PGA score: 3) at baseline than mild subjects (PGA score: 2) in Locoid[®]. This may be due to the fact that subjects with mild AD had to reach clear, while moderate subjects could reach clear or almost clear to achieve success status. The success rate in subjects with %BSA below the median was slightly lower than that of subjects with %BSA above the median in the Locoid[®] arm.

Table 17: PGA Number (%) Successes by Baseline Disease Severity

| | | Locoid [®] Lotion N=139 | Vehicle N=145 |
|---------------|-----|-------------------------------------|------------------|
| Baseline PGA | 2 | Total | 65 |
| | | Success (%) | 25 (38%) |
| | 3 | Total | 74 |
| | | Success (%) | 43 (58%) |
| | 4 | Total | 0 |
| | | Success (%) | 0 |
| Baseline %BSA | ≤20 | Total | 75 |
| | | Success (%) | 34 (45%) |
| | >20 | Total | 64 |
| | | Success (%) | 34 (53%) |

Source: MOD 5, VOL 10, pg. 128, and Reviewer analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor submitted the results of one pivotal study (04-103) conducted in the pediatric population and one supportive study (03-074) in the adult population to support the efficacy and safety claim for Locoid[®] Lotion, 0.1% in the treatment of atopic dermatitis. The sponsor conducted the pivotal study under the protocol that was agreed upon with the Agency in terms of study design and the primary endpoint. Efficacy was evaluated on Day 29 using the proportion of successes based on the PGA score. The difference in the success rates were statistically significant with a p-value of less than 0.0001 in the Pivotal study. The efficacy result were relatively consistent across subgroups and investigative sites. The protocol defined change from baseline in pruritus at Day 29 as the secondary endpoint which was also statistically significant with a p-value less than 0.0001.

The supportive study results were consistent with the findings from the pivotal study. The difference in the success rates were statistically significantly with a p-value of less than 0.0001.

5.2 Conclusions and Recommendations

Locoid[®] Lotion, 0.1% has been demonstrated to be statistically superior to vehicle in one pediatric pivotal study (04-103) and one adult supportive study (03-074) in the treatment of

atopic dermatitis. Efficacy was evaluated using the success rate based on the Physician Global Assessment (PGA) score at Day 29. Table 7 presents the results of the primary endpoint. The differences in the success rates was statistically significant with a p-value of less than 0.0001.

Table 18: Efficacy Results - Number (Proportion) of successes on PGA

| Study | Locoid [®] Lotion | Vehicle | p-value* |
|---------------------|----------------------------|----------|----------|
| | N=139 | N=145 | |
| 04-103 (Pivotal) | 68 (49%) | 35 (24%) | <0.0001 |
| 03-074 (Supportive) | 84 (56%) | 49 (33%) | <0.0001 |

* p-value was calculated using CMH test, stratified by pooled sites

Source: MOD 5, VOL 10, pg. 53 and MOD 5, VOL 3, pg. 56

The adverse event rates were higher in vehicle subjects than Locoid[®] subjects. The most common adverse events were application site AEs, which was reported in approximately 8% of the subjects. The next common adverse event was nasopharyngitis.

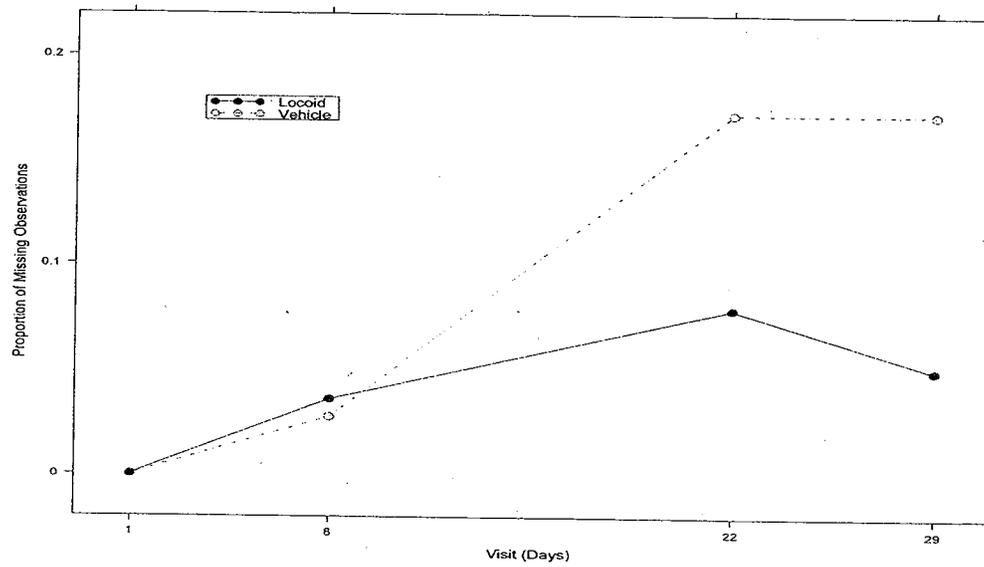
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APPENDIX

A.1 Proportions of Missing Observations

Figure 3 presents the proportion of missing observations in each treatment arm over time.

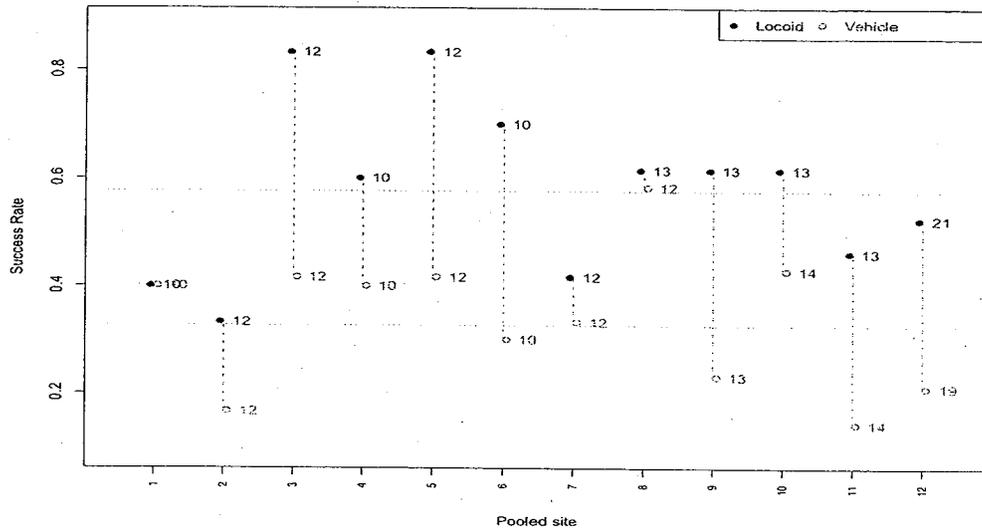
Figure 3: Proportion of Missing Observations Over Time



The number of missing observations at Day 29 were a total of 32 (11.3%) subjects. Locoid[®] had a slightly larger proportion of missing observations at Day 8. However, at later visits, the vehicle arm had larger proportions of missing data.

A.2 Supportive Study (03-074) Efficacy Results by Center

Figure 4: Efficacy by Pooled Sites



This study involved 20 investigators, all from the United States. Each investigator enrolled between 6 to 24 subjects. Sites with smaller enrollment were combined in the same way as the pivotal study. There were a total of 12 pooled investigative sites. Figure 4 presents the treatment success rate and the number of subjects enrolled in each pooled site by treatment. The success rate of both arms appeared to be relatively consistent across pooled sites, and therefore the results do not seem to be driven by extreme sites. The Breslow-Day test results also supported this conclusion with a p-value of 0.6735.

A.3 Subgroup Analysis Plots

Figure 5: Efficacy by Gender

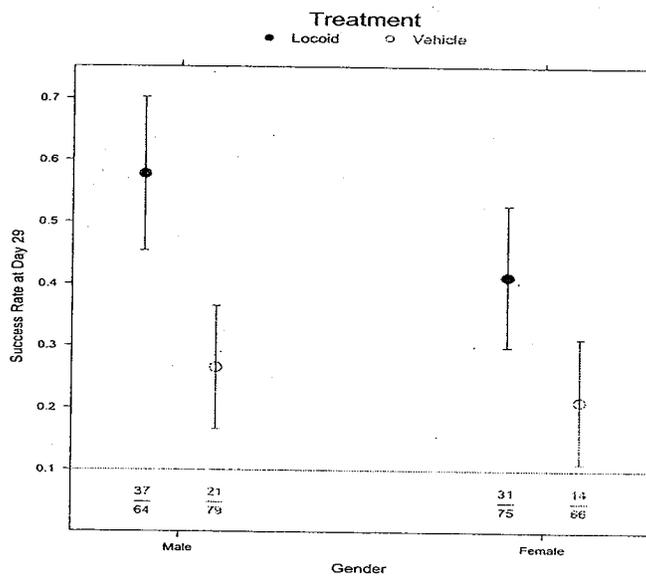


Figure 6: Efficacy by Race

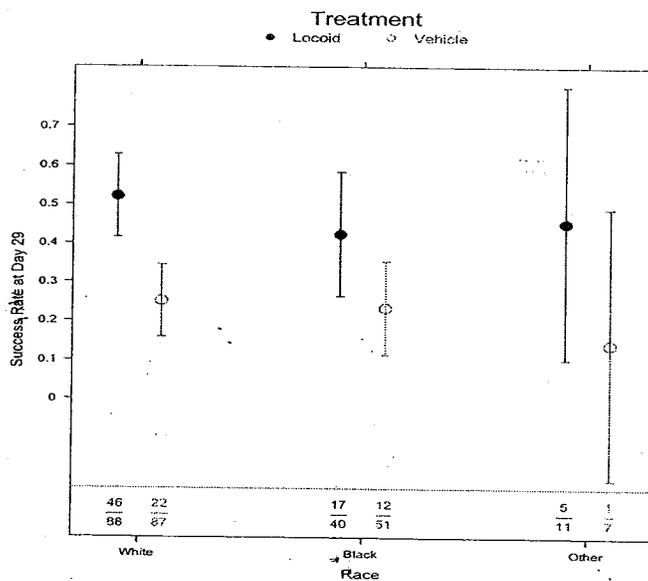
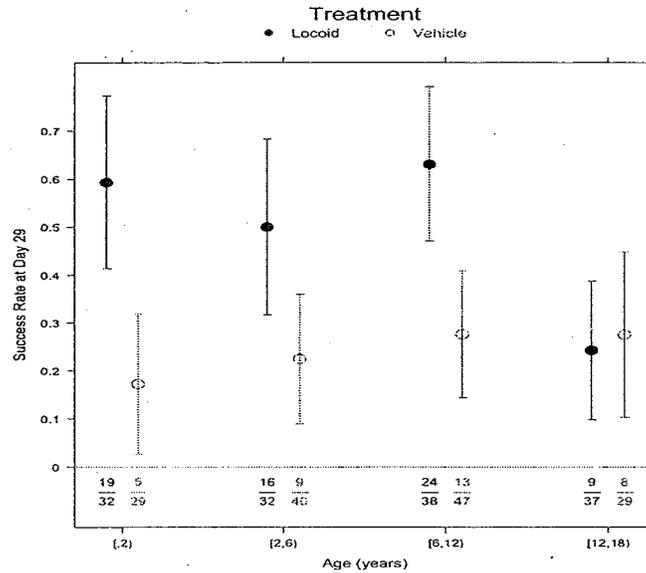


Figure 7: Efficacy by Age



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March 14, 2007

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