CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

US Department of Health and Human Services
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Statistical Review and Evaluation

New Drug Application

Clinical Studies

NDA/Serial Number:	21-978/N-000
Drug Name:	Desonide Foam, 0.05%
Indication(s):	Atopic dermatitis
Applicant:	Connetics Corporation
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Contents

1 Executive Summary

1.1 Conclusions and Recommendations

Desonide foam, 0.05% was statistically superior to its vehicle in a single study (DES.C.301) in the treatment of atopic dermatitis. Efficacy was demonstrated after 4 weeks of treatment. At Week 4, 39% of Desonide subjects were successes versus 9% of vehicle subjects. The primary endpoint and all secondary endpoints were statistically significant with p-values less than 0.0001 for each endpoint.

The adverse event rates were similar on Desonide and vehicle arms, where the vehicle arm's rate was marginally higher than that of Desonide arm. The most common adverse event was upper respiratory tract infection, and was reported by approximately 8% of the subjects. The next common adverse event was application site burning.

1.2 Brief Overview of Clinical Studies

The sponsor conducted one Phase 3, multi-center (17 sites in the United States) study (DES.C.301) evaluating the safety and efficacy of Desonide Foam, 0.05% versus its vehicle in the treatment of adolescent and pediatric subjects with mild to moderate atopic dermatitis. Subjects in the study were evaluated for up to 7 weeks, 4 weeks of treatment and 3 weeks of post-treatment follow-up. A total of 581 subjects were randomized in a 2:1 ratio to receive Desonide Foam, 0.05% or vehicle. The primary endpoint was the proportion of subjects who had (i) Investigator's Static Global Assessment (ISGA) score of clear or almost clear (0 or 1) at Week 4 and a minimum improvement in the ISGA score of two grades from Baseline to Week 4; and (ii) score of 0 or 1 for both erythema and induration/population at Week 4.

The sponsor previously conducted a Phase 2 study (DES.C.202). A total of 106 subjects were randomized in a 2:1 ratio to receive Desonide Foam 0.05% or vehicle. The primary and secondary endpoints were identical to that of the Phase 3 study.

1.3 Statistical Issues and Findings

The sponsor has conducted a single study that demonstrated that Desonide foam, 0.05% is superior to its vehicle in the treatment of atopic dermatitis, by a large margin. The study results were robust and consistent across investigational sites and subgroups. The sponsor conducted the study under the protocol that was agreed upon with the Agency in terms of study design and primary endpoints. The Agency agreed at the Pre-IND/End of Phase 2 meeting (3/30/2004) that one acceptable pathway would be to demonstrate efficacy in a single robust, highly statistically significant study. The primary endpoint was the proportion of success, where success was defined based on the ISGA, erythema, and induration/papulation scores at Week

4. The difference in the success rates were strongly statistically significant (p-value<0.0001). The protocol defined three secondary endpoints that were based on sum of symptoms score, pruritus score, and ISGA score. Desonide was superior to the vehicle for all three secondary endpoints. Subjects were followed for 3 weeks post-treatment. The Desonide arm success rate decreased considerably after the treatment period ended at Week 4, whereas the vehicle success rate continued to increase marginally post-treatment.

2 INTRODUCTION

2.1 Overview

Desonide is a synthetic corticosteroid. Desonide at a concentration of 0.05% is the active ingredient of 10 FDA-approved drugs (Tridesilon, DesOwen, and several generics) for topical application in three dosage forms: cream, ointment, and lotion. The sponsor obtained the right of reference to NDAs 17-010 and 17-426, Tridesilon Cream and Tridesilon Ointment, currently marketed by Clay Park Labs, Bronx, New York. The sponsor referenced the nonclinical and clinical safety data filed in NDAs 17-010 and 17-426 in support of Desonide Foam. In the current application of Desonide Foam, 0.05% , the sponsor is seeking an indication of mild to moderate atopic dermatitis in patients from 3 months to 17 years of age, applied topically twice daily for four weeks.

The protocol for the Phase 3 study (DES.C.301) was discussed in an End of Phase 2 meeting held on March 30, 2004 and was evaluated as Special Protocol Assessment (SPA) in June 2004. At the End of Phase 2 meeting, the sponsor was advised that three Phase 3 pathways could be followed, which were

1. two independent, double-blind, vehicle controlled studies,
2. one 3-arm study demonstrating superiority of Desonide foam to vehicle and non-inferiority to an approved Desonide comparator,
3. one very persuasive, robust, double-blind, vehicle controlled study that is highly statistically significant with no major flaws and consistent results across centers and subgroups.

The 'one very persuasive study' option was given primarily because Desonide Foam, 0.05% had the same strength (0.05%), application route (topical) and frequency (twice daily) as previously FDA-approved Desonide products. The sponsor submitted a single Phase 3 study as SPA, which reflected the selection of the third option given above. Through the meeting and SPA review, the sponsor and the Division came to an agreement on endpoints and most aspects of the study design. The sponsor also conducted a Phase 2 study (DES.C.202) to get initial treatment effect estimates. Table 1 lists the clinical study programs. This review evaluates the Phase 3 efficacy and safety studies and briefly summarizes results from the Phase 2 study.

Table 1: Clinial Study Program

Study	Type	Number of Subjects		
		Desonide	Vehicle	Total
DES.C.202	Phase 2	72	34	106
DES.C.301	Phase 3	387	194	581

2.2 Data Sources

This reviewer evaluated the sponsor's clinical study reports and clinical summaries, as well as the proposed labeling. This submission was submitted in CTD format and was entirely electronic. The datasets used in this review are archived at \\Cdsesub1\n21978\N_000\2005-11-18\m5\53-clin-stud-rep\537-crf-ipl\crt\datasets\301 and \\Cdsesub1\n21978\N_000\2005-11-18\m5\53-clin-stud-rep\537-crf-ipl\crt\datasets\202.

3 Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study Design

The sponsor conducted a Phase 3 study (DES.C.301) to evaluate the safety and efficacy of Desonide Foam, 0.05% in the treatment of mild to moderate atopic dermatitis. Protocol DES.C.301 was evaluated as a Special Protocol Assessment in June 2004. This study was designed as multicenter, double blind, vehicle controlled, and randomized. The treatment duration was 4 weeks with a 3 week follow-up period. The study was conducted in the United States between August 2004 and June 2005. The study planned to enroll a total of 570 subjects from approximately 10 to 15 centers. The actual study enrollment was 581 subjects from 17 centers. The submission entry criteria included subjects from 3 months to 17 years of age, with mild to moderate atopic dermatitis assessed by Investigator's Static Global Assessment (ISGA) (score 2 or 3), whose sum of score for erythema, induration/papulation, and oozing/crusting was greater or equal to 4, and involvement body surface area (%BSA) was greater or equal to 5%.

The enrolled subjects were randomly assigned in a 2:1 ratio to Desonide Foam, 0.05% and vehicle groups. The randomization resulted in 387 and 194 subjects for Desonide Foam, 0.05% and vehicle arms, respectively. The subject caregivers were instructed to apply the smallest amount of medication to just cover all areas affected by atopic dermatitis and to apply not more than twice daily for 4 weeks. Clinical evaluations were conducted at Baseline, Weeks 2, 4, and 7.

Week 4 was the primary time point for efficacy assessment.

For efficacy evaluation, the following endpoints were specified in the protocol.

- Primary: Proportion of subjects who have
  - ISGA score of clear or almost clear (0 or 1) at Week 4 and a minimum improvement of 2 grades from Baseline to Week 4 (or end of treatment), **and**
  - a score of 0 or 1 for erythema at Week 4, **and**
  - a score of 0 or 1 for induration/papulation at Week 4.
- Secondary:
  - Mean percent reduction in the sum of scores of erythema, induration/papulation, lichenification, and scaling from Baseline to Week 4 (or end of treatment)
  - The proportion of subjects who have a pruritus score of 0 at Week 4 (or end of treatment)
  - The proportion of subjects who have an ISGA of 0 or 1 at Week 4 (or end of treatment) and a minimum improvement in the ISGA score of 2 grades from baseline to Week 4 (or end of treatment).

The sponsor denoted the first secondary endpoint as the principal secondary endpoint and added oozing/crusting to the sum of scores to be evaluated in the submission. This change was partially in response to Agency comments and was done via a protocol amendment dated July 9, 2004, which was before the first subject was enrolled (8/31/04). The scoring systems used to assess efficacy in the primary endpoint (ISGA, erythema, and induration/papulation scores) were based on a 5-point scale, defined as the following.

ISGA:

0	**Clear**:	Minor residual discoloration; no erythema or induration/papulation, no oozing/crusting
1	**Almost Clear**:	Trace faint pick erythema, with almost no induration/papulation, and no oozing/crusting
2	**Mild**:	Faint pink erythema, with mild induration/papulation and no oozing/crusting
3	**Moderate**:	Pink-red erythema with moderate induration/papulation and some oozing/crusting
4	**Severe**:	Deep or bright red erythema with severe induration/papulation with oozing/crusting.

Erythema:

0	**Absent**:	No erythema present (may be minor discoloration)
1	**Minimal**:	Faint pink, barely apparent
2	**Mild**:	Pink-red, noticeable
3	**Moderate**:	Pink-red, easily noticeable
4	**Severe**:	Deep or bright red, may feel warm to the touch

Induration/Papulation:

0	**Absent**:	No evidence of elevation
1	**Minimal**:	Barely perceptible elevation
2	**Mild**:	Perceptible but not extensive elevation
3	**Moderate**:	Marked and somewhat extensive elevation
4	**Severe**:	Marked and extensive elevation.

The protocol and submission defined the intent-to-treat (ITT) population as all subjects who were randomized and received the study drug. Subjects were excluded from the per-protocol (PP) population if they missed more than a total of 10 applications at any time or six consecutive applications of the study medication, or did not have efficacy evaluations at Baseline and Week 4 visits, or used prohibited medications at any time during the treatment period. The ITT and PP populations were analyzed for efficacy, where ITT analysis was the primary.

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

- The success rate was analyzed with the Cochran-Mantel-Haenszel (CMH) test stratified by investigational center. The center by treatment interaction was tested using the Breslow-Day test at a significance level of 0.1.

- The principal secondary endpoint, the mean percent reduction in the sum of scores analysis was based on an ANOVA model with terms for treatment, center, and treatment by site interaction.

- The other secondary endpoints (proportion of subjects with pruritus score of 0; and proportions of subjects with ISGA score of 0 or 1 with a minimum improvement of 2 grades) were analyzed using CMH test, stratified by center.

- Last-Observation-Carry-Forward (LOCF) was used to impute missing values in the efficacy endpoint. In addition to the LOCF approach, a sensitivity analysis based on multiple imputations using sequential generalized logistic models. Separate generalized logistic models were specified for each visit that had missing data. Logistic models for the dependent variable with the least missing data was estimated first and proceeded to the dependent variable with the most missing data.

- The target number of subjects per site was at least 30 subjects (20 in the Desonide Foam group and 10 in the vehicle foam group). Sites with smaller enrollment were combined based on geographical location and climate similarities. According to the protocol, combination of the investigative sites was completed prior to unblinding the data.

  Study sites were pooled into 11 investigational groups, which were used in the efficacy analyses. Table 2 presents the pooled sites and the number of subjects in each site before pooling.

Table 2: Enrollment by pooled sites

Pooled Site	Original Site	Number of Subjects	Pooled Site	Original Site	Number of Subjects
1	1, 5	32, 12	7	9	57
2	3	43	8	11	50
3	4	45	9	12, 13, 16	24, 19, 13
4	6	44	10	14	55
5	7	60	11	2, 15, 17	21, 41, 8
6	8, 10	28, 28			

Source: Reviewer analysis

3.1.2 Subject Disposition

The study enrolled a total of 518 subjects from 17 study sites and randomized them in a 2:1 ratio to treatment and vehicle arms. Thus, 387 subjects were randomized to Desonide arm and 194 to the vehicle arm. Table 3 presents the reasons for study discontinuation.

Table 3: Reason for Study Discontinuation

	Desonide N=387	Vehicle N=194
Subjects who discontinued	**33 (9%)**	**54 (28%)**
Reason		
Adverse Event	2 (5%)	17 (9%)
Non-Compliance	6 (2%)	3 (2%)
Disease Progression	3 (1%)	18 (9%)
Subject Request to Withdraw	3 (1%)	12 (6%)
Death	1 (<1%)	0 (0%)
Other	18 (5%)	4 (2%)

Source: Study report 53512-des-c-301.pdf, pg. 41

The number of subjects who discontinued the study was higher in the vehicle arm than the Desonide arm, at 33 (9%) and 54 (28%) for Desonide and vehicle arms, respectively. The most common reason for study discontinuation in the Desonide arm was 'other'. Out of the 18 patients whose reason for discontinuation was 'other', 1 subject misunderstood the visit time lines, 1 subject was 4 weeks late for Visit 3, and the remaining 16 were lost to follow-up. For the vehicle arm, disease progression (18 subjects) and adverse events (17 subjects) were the most common reasons for discontinuation. The reasons for the 3 subjects request for discontinuation in the Desonide arm were worsening of condition, inconvenience, and subject not being able to make visits. In the vehicle arm, 3 subjects requested to withdraw due to worsening of condition, 7 subjects due to lack of efficacy, and 1 subject due to lack of time.

3.1.3 Baseline and Demographic Data

Table 4 presents the Baseline demographic data. The Baseline demographic variables were generally balanced across treatment arms. The average age of the subjects was approximately 6.9 years and the age range was from 3.6 months to 18 years. Desonide arm had slightly more male subjects (51%) than females, whereas the vehicle arm has more females subjects (54%) than males. Approximately half of the subjects were Caucasian on both arms. Race was relatively balanced across treatment arms.

Table 4: Baseline Demographic Data

	Desonide Foam N=387	Vehicle N=194
Age(in years)		
mean (std)	7.0 (4.8)	6.8 (4.9)
median	6.2	5.4
min,max	(0.3,18.0)	(0.4,18.0)
Gender		
Male	198 (51%)	90 (46%)
Female	189 (49%)	104 (54%)
Race		
Caucasian	191 (49%)	100 (52%)
African-American	94 (24%)	49 (25%)
Hispanic	66 (17%)	32 (16%)
Asian	17 (4%)	6 (3%)
Other	19 (5%)	7 (4%)

Source: Study report 53512-des-c-301.pdf, pg.44

Table 5 presents the Baseline ISGA scores and the extent of atopic dermatitis (%BSA). The

Baseline severity scores, the ISGA score and Body surface area (%BSA), were fairly balanced between the Desonide foam and vehicle arms. Desonide arm had a slightly higher proportion of subjects with moderate severity and a marginally higher mean %BSA score than the vehicle arm. Although the study population was mild to moderate atopic dermatitis, one subject with ISGA score of 4 was enrolled in the vehicle arm. All subjects had atopic dermatitis on at least 5% of their body surface. The median %BSA was 15% and 13%, and the maximum surface area was 97% and 90% for Desonide and vehicle arms, respectively.

Table 5: Baseline Severity

	Desonide Foam N=387	Vehicle N=194
Investigator's Static Global Assessment Score		
2	145 (37%)	74 (38%)
3	242 (63%)	119 (61%)
4	0 (0%)	1 (1%)
Extent of Atopic Dermatitis (%BSA)		
mean (std)	21 (18.7)	19.8 (17.5)
median	15	13
min,max	(5,97)	(5,90)

Source: Study report 53512-des-c-301.pdf, pg.45

3.1.4 Primary Efficacy Endpoints

3.1.4.1 *ITT Analyses*

The protocol defined success as subjects who had

- ISGA score of 0 or 1 at Week 4, with a minimum improvement of 2 grades from Baseline to Week4; **and**
- Erythema score of 0 or 1 at Week 4; **and**
- Induration/papulation score of 0 or 1 at Week 4.

Table 6 presents the primary efficacy results in the intent-to-treat (ITT) population. At Week 4, the primary time point, 39% of the Desonide foam subjects reached success status, while 9% of the vehicle arm 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 Desonide foam at Week 4.

Since the primary endpoint is defined as success only when several conditions are met, this reviewer compared the success rate of each component of the primary endpoint. Table 7 presents

the success rates of each component of the primary endpoint. Differences between the Desonide and treatment arms in all three components of the primary endpoint were highly statistically significant with p-values less than 0.0001.

Table 6: Primary Efficacy Endpoint Results (ITT)

	Desonide Foam N=387	Vehicle N=194	p-value*
Success	152 (39%)	18 (9%)	<0.0001

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

Source: Study report 53512-des-c-301.pdf, pg. 54

Table 7: Components of Primary Endpoint Results

	Desonide Foam N=387	Vehicle N=194	p-value*
ISGA†	157 (41%)	18 (9%)	< 0.0001
Erythema‡	262 (68%)	69 (36%)	< 0.0001
Induration/Papulation‡	268 (69%)	73 (38%)	< 0.0001

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

† Success is defined as score of 0 or 1 at Week 4 with a minimum improvement of 2 grades from Baseline to Week 4

‡ Success is defined as score of 0 or 1 at Week 4

Source: Reviewer analysis

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 analyses of the previous section. This reviewer 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.

The number of missing subjects at Week 4 was a total of 73 observations (12.6%), 28 (7%) and 45 (23%) in Desonide and vehicle arms, respectively. Thus, the vehicle arm had a larger number of drop-outs than the Desonide arm. Imputing the missing data as successes is a conservative approach, since the vehicle arm has more missing data and the most common reason for drop-out was due to lack of efficacy, while that of the Desonide arm was lost to follow-up. However,

Table 8: Sensitivity Analyses on Primary Endpoint

	Desonide Foam N=387	Vehicle N=194	p-value*
Imputed subjects‡	28 (7%)	45 (23%)	
Success†	179 (46%)	62 (32%)	0.0009
Success††	151 (39%)	17 (9%)	< 0.0001

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

‡ Number of missing subjects at Week 4

† Missing data imputed as successes

†† Missing data imputed as failures

Source: Reviewer analysis

even using this approach, the difference in proportion of success in the two arms was statistically significant with a p-value of 0.0009, in favor of the treatment arm. The second analysis (imputing missing as failure) results are similar that using LOCF. The sensitivity analyses ensures that the statistically significant results 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 had missed more than a total of 10 applications at any time or 6 consecutive applications of study medication, subjects who did not have efficacy evaluations at the Baseline and Week 4 visits, and subjects who have used prohibited medications at any time during the treatment period. A total of 100 subjects (17%) were excluded from the PP population, 41 subjects (11%) and 59 subjects (30%) in the Desonide and vehicle arms, respectively. The most common reason for exclusion in the vehicle arm was due to the subject missing more than a total of 10 applications (51 subjects) followed by no efficacy assessments at Baseline or Week 4 (6 subjects). For the Desonide arm, the subjects were excluded due to the two reasons above with equal frequency (18 subjects). Note that some subjects were excluded for multiple reasons. Table 9 presents the results of the primary endpoint analysis at Week 4 based on the per protocol population.

The proportion of successes in the per protocol population was higher for both arms than the ITT population at 42% and 13%, Desonide and vehicle arms, respectively. The difference in the proportion of success of the two arms was strongly 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 Desonide foam over vehicle. The analyses results of each component of the primary endpoint based on the PP population can be found in the Appendix (Table 17).

Table 9: Primary Efficacy Endpoint Results (PP)

	Desonide N=346	Vehicle N=135	p-value*
Success	147 (42%)	17 (13%)	<0.0001

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

Source: Study report 53512-des-c-301.pdf, pg. 63

3.1.5 Secondary Efficacy Endpoints

The secondary endpoints defined in the protocol were

- Mean percent reduction in the sum of scores of erythema, induration/papulation, lichenification, and scaling from Baseline to Week 4 (or end of treatment)
- The proportion of subjects who have a pruritus score of 0 at Week 4 (or end of treatment)
- The proportion of subjects who have an ISGA of 0 or 1 at Week 4 (or end of treatment) and a minimum improvement in the ISGA score of 2 grades from baseline to Week 4 (or end of treatment).

The sponsor's estimation of the first secondary endpoint (Source: 53512-des-c-301.pdf, pg. 154) was based on a population that excluded 24 subjects from the ITT population, 18 and 6 subjects from Desonide and vehicle arms, respectively. The rational of excluding these subjects were not stated in the submission. The sponsor's analysis resulted in mean percent reductions in the sum of scores for clinical signs of 60.0% and 20.9% for Desonide foam and vehicle arms, respectively. In this review, the first secondary (principal secondary) endpoint was reanalyzed using the same population that was used for the primary endpoint analysis, thus the ITT population using LOCF to impute missing observations at Week 4. Table 10 presents the results of the principal secondary endpoint using the ITT population.

This reviewer's analysis using the ITT population resulted in mean percent reductions of 57.2% and 20.2% for Desonide and vehicle arms, respectively. These results are marginally smaller than those of the sponsor for both arms. The difference in the mean percent reduction from Baseline to Week 4 of the two arms are statistically significant with a p-value of less than 0.0001.

The sponsor analyzed the additional secondary endpoints (the proportion of subjects with a pruritus score of 0 at Week 4: and the proportion of subjects with modified success at Week 4) based on the ITT population which is presented in Table 11. Modified success was defined as subjects who had an ISGA score of 0 or 1 at Week 4 (or end of treatment) and a minimum improvement in the ISGA scores of 2 grades from Baseline to Week 4.

Table 10: Mean Percent Reduction in the Sum of Scores for Clinical Signs from Baseline to Week 4 (ITT)

	Desonide Foam N=387	Vehicle N=194	p-value†
Baseline	9.6 (2.8)*	9.7 (2.7)	
Week 4/End of Treatment	4.1 (3.8)	7.8 (4.6)	
Percent Reduction from Baseline	57.2 (37.5)	20.2 (40.5)	< 0.0001

* Numbers in parentheses represent the standard deviation

† p-value is derived from a parametric ANOVA model with terms for treatment and pooled sites

Source: Reviewer analysis

Table 11: Additional Secondary Endpoints (ITT)

	Desonide Foam N=387	Vehicle N=194	p-value *
Pruritus Score of 0	133 (34%)	19 (10%)	<0.0001
Modified Success†	157 (41%)	18 (9%)	<0.0001

* p-value is derived from Cochran-Mantel-Haenszel test stratified by pooled sites.

† Modified Success is defined as the proportion of subjects who have an ISGA score of 0 or 1 at Week 4 and a minimum improvement in the ISGA score of 2 grades from Baseline to Week 4.

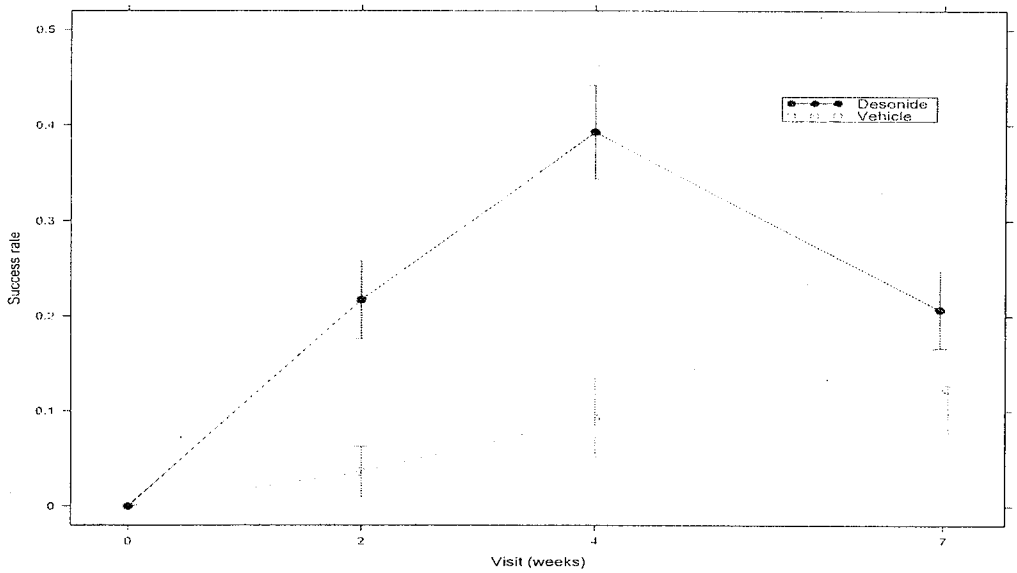
Source: Reviewer analysis and Study report 53512-des-c-301.pdf, pg. 72 and pg. 71

Thirty four percent of the Desonide arm and 10% of the vehicle arm had a pruritus score of 0 at Week 4, using LOCF to impute the missing observations per protocol. One subject on the vehicle arm had a pruritus score of 0 at Baseline, but did not have an assessment at Week 4. The sponsor's analysis imputed the missingness as failure (score greater than 0). Thus, Table 11 shows one more score 0 in the vehicle arm than the sponsor's analysis. However, the discrepancy does not alter the conclusion that the difference between the two arms' proportion of subjects who had a score of 0 in pruritus score is statistically significant, with a p-value less than 0.0001. The difference of the proportion of subjects with modified success is also highly significant with a p-value less than 0.0001, which was discussed as a component of the primary endpoint in Table 7.

3.1.6 Efficacy Results over Time

Subjects were followed for a total of 7 weeks, including a 3 week post-treatment follow-up period. Subjects were evaluated at Baseline, Week 2, Week 4 (End of Treatment), and Week 7 (3 Week post-treatment). This reviewer presents the primary endpoint success rate over time in Figure 1. Along with the success rate, unadjusted 95% confidence intervals are presented to show the variability of the success rates at each visit.

Figure 1: Success over time

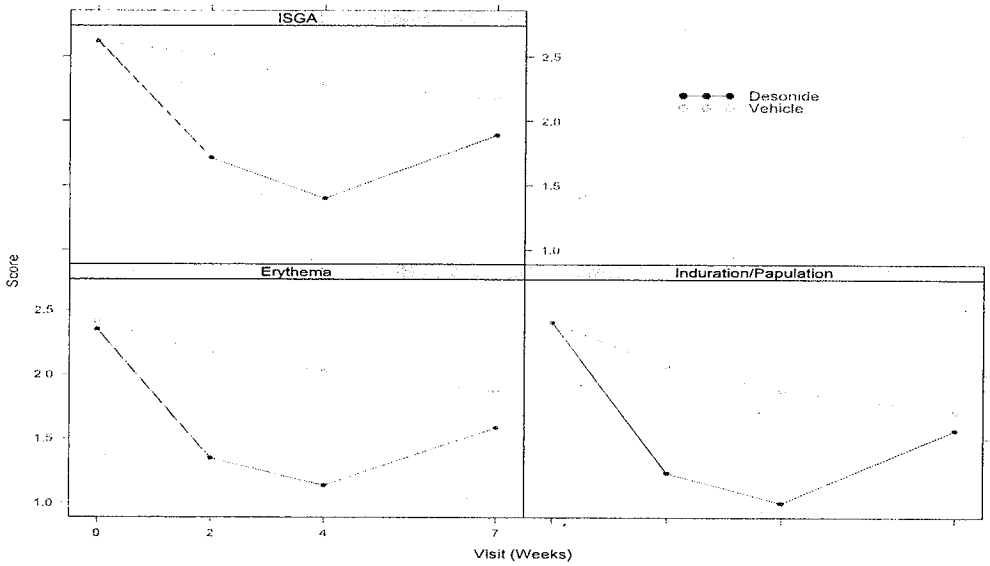


The success rate of Desonide foam continued to steeply increase throughout the treatment period, but decreased considerably after the treatment period ended at Week 4. The success rate of Desonide foam was 21.7% and 20.7% at Week 2 and Week 7, respectively, (Week 4 success rate was 39.3%) indicating a lower response rate at 3 weeks post-treatment than 2 weeks into the treatment (see Appendix on page 24). The vehicle arm success rate increased throughout the treatment period, however at a much smaller degree than the treatment arm, and continued to increase marginally during the follow-up period. Although the Desonide arm success rate decreased post-treatment, the success rate in the Desonide foam arm remained higher than that of the vehicle arm at Week 7 at 20.7% and 12.4%, Desonide and vehicle arms, respectively. The 95% confidence intervals of the success rates do not overlap during the treatment period, Desonide group being superior to the vehicle. However, the confidence intervals overlap slightly at the post-treatment evaluation.

Figure 2 presents the scores of the three elements that form the success criteria (ISGA, erythema, and induration/papulation) over time. Note that higher scores indicate more severe

symptoms. The scores of the Desonide foam in all three elements continued to decrease until the end of treatment and increased after that, which is consistent with the overall success rate. The scores of the vehicle arm are also consistent to the overall success rate, which decreased at a more marginal degree than the treatment arm but continued to decrease post-treatment.

Figure 2: ISGA, Erythema and Induration/Papulation scores over time

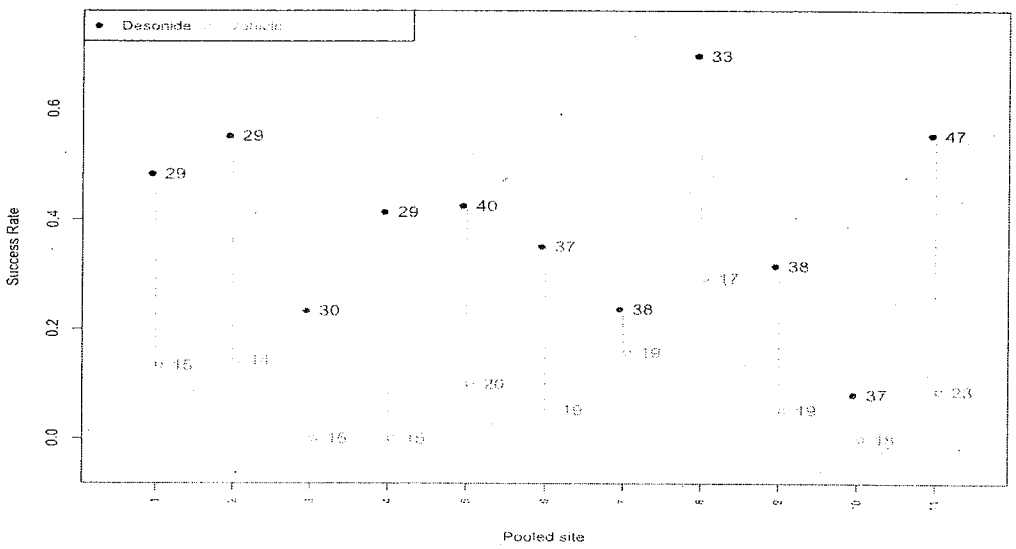


3.1.7 Efficacy Results by Center

This study involved 17 investigators, all from the United States. Each investigator enrolled between 8 to 60 subjects. Sites were pooled based on geographical and climate similarities if enrollment was less than 30 subjects per protocol (20 in Desonide foam group and 10 in vehicle arm). According to the sponsor, pooling was done before unblinding of the data. There were 11 pooled investigative sites.

This reviewer presented the success rate and number of subjects enrolled in each pooled site by treatment in Figure 3. The success rates 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 0.6388.

Figure 3: Efficacy by pooled sites



3.2 Efficacy Results from Phase 2 Study (DES.C.202)

The sponsor conducted a small Phase 2 study that randomized 106 subjects to Desonide Foam, 0.05% or vehicle group in a 2:1 ratio, 72 and 34 subjects for Desonide and vehicle arms, respectively. The primary and secondary endpoints were identical to the Phase 3 study. The subject inclusion criteria, (ISGA score of 2 or 3; a sum of scores for erythema, induration/papulation, and oozing/crusting of $\geq$ 4; and an involvement of $\geq$ 5% total body surface area) were also identical to the Phase 3 study. Table 12 presents the point estimates of the primary endpoint analysis from the Phase 2 trial.

Table 12: Primary Endpoint Analysis (Phase 2)

	Desonide Foam N=72	Vehicle N=34
Success[†]	39 (54%)	4 (12%)

[†] Success was defined identically to the primary endpoint of the Phase 3 study.

Source: Study report 53511-des-c-202.pdf, pg. 52

The success rate in the Desonide arm (54%) was much greater than that of the vehicle arm (12%) and also larger than the Desonide arm success rate (39%) of the Phase 3 study. Although

Table 14: Application Site Adverse Events

	Desonide N=387	Vehicle n=194	Total N=581
Application site AEs	**22 (6%)**	**27 (14%)**	**49 (8%)**
Conditions			
Atrophy	5 (1%)	0 (0%)	5 (1%)
Burning	11 (3%)	15 (8%)	26 (4%)
Dermatitis	2 (1%)	1 (1%)	3 (1%)
Desquamation	0 (0%)	2 (1%)	2 (0%)
Erythema	1 (0%)	3 (2%)	4 (1%)
Pigmentation changes	1 (0%)	2 (1%)	3 (1%)
Reaction	3 (1%)	6 (3%)	9 (2%)
Urticaria	0 (0%)	2 (1%)	2 (0%)

Source: Study report 53512-des-c-301, pg. 101

The most common adverse event concerning application site was application site burning. A larger proportion of subjects on the vehicle arm (8%) experienced this event than the Desonide arm (3%). With the exception of atrophy, which 5 subjects on the Desonide arm and none on the vehicle arm experienced, more vehicle subjects experienced local adverse events than Desonide subjects.

4 Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Table 15 presents the success rates by gender, race and age groups based on the ITT population. Efficacy does not appear to be affected by gender, race, and age. Male and female subjects in the treatment arm had similar success rates, which was also consistent across age categories. The success rate in the Hispanic group was slightly higher than that of other groups. Nevertheless, the subgroup analysis supports the claim that the Desonide arm success rate is superior to that of the vehicle arm across subgroups.

Table 15: Subgroup Analysis (ITT)

			Desonide Foam N=387	Vehicle N=194
Gender	Male	Total	198	90
		Success (%)	78 (39%)	12 (13%)
	Female	Total	189	104
		Success (%)	71 (39%)	6 (6%)
Race	Caucasian	Total	191	100
		Success (%)	65 (34%)	5 (5%)
	African-American	Total	94	49
		Success (%)	27 (29%)	6 (12%)
	Hispanic	Total	66	32
		Success (%)	40 (61%)	4 (13%)
	Other	Total	36	13
		Success (%)	20 (56%)	3 (23%)
Age	[12 yrs, 18 yrs)	Total	76	34
		Success (%)	29 (38%)	4 (12%)
	[6 yrs, 12 yrs)	Total	123	53
		Success (%)	48 (39%)	7 (13%)
	[3yrs, 6 yrs)	Total	86	47
		Success (%)	35 (41%)	3 (6%)
	[3 mths, 3 yrs)	Total	102	60
		Success (%)	40 (39%)	4 (7%)

Source: Study report 53512-des-c-301.pdf, pg. 59-61

4.2 Other Special/Subgroup Populations

The proportion of success rate was explored by Baseline disease severity. The sponsor analyzed success rate at Week 4 by Baseline ISGA 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$\leq$ 14 or %BSA$>$ 14, where 14 was the median %BSA of all subjects. Table 16 presents the success rate by baseline severity.

Success rates were slightly higher for subjects with moderate atopic dermatitis (ISGA 3) at Baseline than mild subjects (ISGA 2). This may be due to the fact that subjects with mild atopic dermatitis 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 higher than that of subjects with %BSA above the median.

Table 16: Subgroup Analysis: Baseline Disease Severity

			Desonide Foam N=387	Vehicle N=194
Baseline ISGA	2	Total	198	90
		Success (%)	44 (30%)	3 (4%)
	3	Total	242	120†
		Success (%)	108 (15%)	15 (13%)
Baseline %BSA	≤ 14	Total	190	102
		Success (%)	87 (46%)	10 (10%)
	> 14	Total	197	92
		Success (%)	65 (33%)	8 (9%)

† The subject with baseline ISGA score of 4 was included in ISGA 3

Source: Study report 53512-des-c-301.pdf, pg.62 and reviewer analysis

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The sponsor submitted the results of one pivotal Phase 3 trial and one Phase 2 trial to support the efficacy and safety claim for Desonide foam, 0.05% in the treatment of atopic dermatitis. The sponsor has conducted a single Phase 3 study that demonstrated that Desonide foam, 0.05% is superior to its vehicle in the treatment of atopic dermatitis, by a large margin. The study results were robust and consistent across investigational sites and subgroups. The sponsor conducted the study under the protocol that was agreed upon with the Agency in terms of study design and primary endpoints. The Agency agreed at the Pre-IND/End of Phase 2 meeting (3/30/2004) that one acceptable pathway would be to demonstrate efficacy in a single robust, highly statistically significant study. The primary endpoint was the proportion of success, where success was defined based on the ISGA, erythema, and induration/papulation scores at Week 4. The difference in the success rates were strongly statistically significant (p-value<0.0001). The protocol defined three secondary endpoints that were based on sum of symptoms score, pruritus score, and ISGA score. Desonide was superior to the vehicle for all three secondary endpoints. Subjects were followed for 3 weeks post-treatment. The Desonide arm success rate decreased considerably after the treatment period ended at Week 4, whereas the vehicle success rate continued to increase marginally post-treatment.

Although the Phase 2 trial was not powered for statistical inference, the results were consistent to the findings from the Phase 3 study. The success rate in the Desonide arm was much

greater than that of the vehicle arm.

5.2 Conclusions and Recommendations

Desonide foam, 0.05% was statistically superior to its vehicle in a single study (DES.C.301) in the treatment of atopic dermatitis. The results from this Phase 3 study were consistent to those of the previously conducted Phase 2 trial. Efficacy was demonstrated after 4 weeks of treatment. At Week 4, 39% of Desonide subjects were successes versus 9% of vehicle subjects. The primary endpoint and all secondary endpoints were statistically significant with p-values less than 0.0001 for each endpoint.

The adverse event rates were similar on Desonide and vehicle arms, where the vehicle arm's rate was marginally higher than that of Desonide arm. The most common adverse event was upper respiratory tract infection, and was reported by approximately 8% of the subjects. The next common adverse event was application site burning.

APPENDIX

Per Protocol Primary Endpoint Components

Table 17: Components of Primary Endpoints (PP)

	Desonide Foam N=346	Vehicle N=135	p-value*
ISGA†	152 (44%)	17 (13%)	
Erythema‡	251 (73%)	60 (44%)	< 0.0001
Induration/Papulation‡	259 (75%)	66 (49%)	< 0.0001

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

† Success is defined as score of 0 or 1 at Week 4 with a minimum improvement of 2 grades from Baseline to Week 4

‡ Success is defined as score of 0 or 1 at Week 4

Source: Reviewer analysis

Table of Efficacy Over Time

Table 18: Table of Efficacy Over Time

Week	Desonide Foam N=387	Vehicle N=194
0	0 (0%)	0 (0%)
2	84 (21.7%)	7 (3.6%)
4	152 (39.3%)	18 (9.3%)
7	80 (20.7%)	24 (12.4%)

Source: Reviewer analysis

Signatures/Distribution List

Primary Statistical Reviewer: Clara Kim, Ph.D.
Date: June 19, 2006

Statistical Team Leader: Mohamed Alosh, Ph.D.

cc:
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DDDP/Walker
DDDP/Kukich
DDDP/Luke
DDDP/Lindstrom
DDDP/Nikhar
DDDP/Cook
DDDP/Harris-Bauerlien
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OBIO/Patrician
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