CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 204141
Supplement #:	Original-1
Drug Name:	Desoximetasone Spray, 0.25%
Indication(s):	Plaque psoriasis
Applicant:	Taro Pharmaceuticals
Date(s):	Stamp date: 6/12/2012
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Keywords: Clinical studies, Superiority trials

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1 EXECUTIVE SUMMARY

The sponsor submitted results of two Phase 3 trials to support the efficacy claim for plaque psoriasis. Desoximetasone spray, 0.25% was statistically superior to vehicle spray in two studies (Studies 0808 and 0914) in the treatment of moderate to severe plaque psoriasis. The protocol-specified co-primary efficacy endpoints were the following:

- proportion of subjects who were a Clinical Success (PGA score of 0 or 1) at Day 28
- proportion of subjects who were a Treatment Success for the Target Lesion (a score of 0 or 1 for each of the three signs, i.e., erythema, scaling and plaque elevation) at Day 28.

Summary of co-primary efficacy results is given in the following table.

Table 1. Sponsor's Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	**Vehicle**	**p-value[3]**
Study 0808			
Clinical Success [1]	18/59 (30.5%)	3/60 (5.0%)	0.0003
Treatment Success [2]	23/59 (39.0%)	4/60 (6.7%)	<0.0001
Study 0914			
Clinical Success [1]	32/60 (53.3%)	11/60 (18.3%)	<0.0001
Treatment Success [2]	32/60 (53.3%)	10/60 (16.7%)	<0.0001

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
(3) P-value is calculated from two-sided continuity corrected Z test.
Source: sponsor's analysis.

2 INTRODUCTION

2.1 Overview

2.1.1 History of Drug Development

The IND was opened on 2/28/2008. The sponsor submitted their Phase 2 protocol DSXS-0808 in SDN 002 on 7/16/2008, and the following statistical comments were sent to the sponsor in an Advice Letter.

> "The sponsor submitted several protocols to the IND under SDN002 (stamp date: 07/16/2008). Based upon the information received, the clinical development of Desoximetasone Spray does not appear to be adequate to prepare for Phase 3. While Protocol DSX-0808 may provide some data to inform the design for Phase 3 trials, it does not fully explore all aspects of dose ranging which would include exploration of dose concentrations, frequency of use, and duration of use. It should be noted that a well-designed Phase 2 dose-ranging trial increases the likelihood of selecting the appropriate dose for confirmatory Phase 3 trials. In addition, it provides estimates of treatment effect(s) to be used in calculation of sample sizes for Phase 3 trials which minimizes the risk of

under powering the Phase 3 trials. As such, the Phase 2 program does not need to be formally powered and does not need to include formal statistical testing as obtaining estimates and establishing trends would be sufficient to plan Phase 3 trials and to confirm study hypotheses. The protocol lists several secondary endpoints which is acceptable for Phase 2 trials. However, in Phase 3 trials, secondary endpoints need to be clinically meaningful and multiplicity adjustments must be included in the protocol to control the Type I error".

On 11/26/2009, the sponsor submitted a dose-ranging Phase 2 protocol, DSXS-0906, for Agency's comments.

On 7/28/2010, the sponsor submitted an amended protocol DSXS-0808 and a new Phase 3 protocol, DSXS-0914, which were identical in study design. The sponsor stated that the amendment incorporated the Agency's recommendation as stated in the Advice Letter dated 7/6/2009, and also provided clarification to the primary endpoint analyses, and multiplicity adjustment for secondary endpoints. It should be noted that while the original protocol DSXS-0808 was a Phase 2 study, the amended protocol was for a Phase 3 trial as noted by the sponsor.

On 7/20/2011, there was a Pre-NDA meeting between the Agency and the sponsor. At that time, the following comments were conveyed to the sponsor.

> "Your studies might lack components of well-designed and conducted clinical trials necessary for establishing efficacy. You indicated that your studies were multicenter trials; however, it is not clear from your protocols or submission the number of centers in each study nor the number of subjects planned and enrolled per center; so that an investigation of site-to-site variability can be made. It is not clear whether randomization was stratified by site to ensure reasonable number of subjects per treatment arm per site so that comparison of the response rates across sites can be made and stratification of the statistical analysis by site is meaningful. Your propose approach for handling missing data might not be scientifically justifiable. In terms of study conduct, you stated in the submission that there were 35 patients common among your trials DSXS-0906 (Phase 2), DSXS-0808 (now Phase 3) and DSXS-0914 (Phase 3). You are reminded that replication of study findings from independent and well-controlled trials needed for establishing an efficacy claim. You should clarify how enrollment of these patients occurred twice and the centers in which enrollment of the same patients in multiple trials occurred, so that an analysis can be carried out to investigate the impact of such double enrollment on the efficacy findings in your trials (which are relatively small to start with – about 120 patients in each".

According to the sponsor's study report, the two Phase 3 trials are identical, and there was one protocol amendment on both protocols, and the amendment occurred prior to study initiation.

- Original protocol (dated 7/2/2010)
- Amendment 1 (dated 7/21/2010)

Details regarding the amendment include clarification of the planned analysis of the primary endpoints and a proposal to conduct a hierarchical testing of the secondary endpoints (see details in Section 3.2.2).

For Study 0808, the first subject was enrolled on 8/31/2010, and the study was completed on 12/2/2010. For Study 0914, the first subject was enrolled on 9/7/2010, and the study was completed on 12/8/2010. An overview of the Phase 3 trials is presented in Table 2.

Table 2: Clinical Study Overview

Study	Study Sites	Study Population	Treatment Arms	Number of Subjects	Dates
0808	US (9 centers)	Age ≥18, ≥10% BSA[(1)], ≥ 7 TLSS[(2)], plaque elevation score ≥3, PGA[(3)] of 3 or 4 at baseline	Desoximetasone, 0.25% spray	59	8/31/2010-12/2/2010
			Vehicle spray	60	
0914	US (9 centers)		Desoximetasone, 0.25% spray	60	9/7/2010-12/8/2010
			Vehicle spray	60	

(1) BSA (Body surface area); (2) TLSS (target lesion severity score); (3) PGA (physician global assessment).
Source: reviewer's table.

2.1.2 Specific Studies Reviewed

In this application, the sponsor submitted results from two identical Phase 3 trials. Both trials enrolled male or female subjects at least 18 years of age with a "definite clinical diagnosis of stable plaque psoriasis" involving ≥10% body surface area (BSA), a combined total lesion severity score (TLSS) of ≥7, a plaque elevation score of ≥3 of the target lesion, and a Physician Global Assessment (PGA) of 3 or 4 at baseline were enrolled.

Table 3. Physician Global Assessment (PGA) scale

0	Clear	No Psoriatic lesions, i.e. no plaque formation; no erythema, no induration, no scaling.
1	Almost clear	No more than minimal scaling or minimal residual erythema. No more than minimal plaque elevation just above normal skin level.
2	Mild	Scaling present although not extensive. Plaque elevation, discernable but not pronounced, erythema generally light red in color.
3	Moderate	Scaling easily observed with red erythema. Plaque elevation distinct and elevated with rounded, sloping edges.
4	Severe	Scaling is coarse and thick. Erythema is dark red. Plaque elevation has hard edges
5	Very severe	Coarse scaling with pronounced cracking and fissures. Erythema is dark red with induration. Plaques are markedly elevated with sharp and hard edges

Source: sponsor's protocol (page 38)

Table 4. Sponsor's Total Lesion Severity Score (TLSS)

Scaling:	
0 = Clear	No evidence of scaling
1 = Almost Clear	Occasional fine scales
2 = Mild	Slight but definite roughness.
3 = Moderate	Moderate roughness, coarse scaling
4 = Severe	Marked roughness, thick scaling
5 = Very Severe	Very thick scales covering extensive areas.
Erythema:	
0 = Clear	No evidence of erythema
1 = Almost Clear	Pink coloration
2 = Mild	Light red coloration
3 = Moderate	Moderate redness, but not dark
4 = Severe	Dark red coloration
5 = Very Severe	Very dark red coloration
Plaque elevation*:	
0 = Clear	No evidence of plaques above surrounding normal skin level
1 = Almost Clear	Minimal plaque elevation. Slight but definite elevation above surrounding normal skin
2 = Mild	Mild plaque elevation
3 = Moderate	Moderate plaque elevation
4 = Marked	Marked plaque elevation
5 = Severe	Severe plaque elevation

Source: sponsor's protocol (page 39)

It should be noted that in the Pre-NDA meeting submission (meeting date: 7/20/2011), the sponsor stated that there are 35 common subjects across the Phase 2 and Phase 3 trials. According to the submitted datasets, 34 of the 35 subjects were common across DSXS-0906 (Phase 2) and DSXS-0808 (Phase 3) trials, and 1 subject was common across DSXS-0906 (Phase 2) and DSXS-0914 (Phase 3) trials. Because there are no common subjects across the two Phase 3 trials, the two Phase 3 trials are considered to be independent trials. However, as a sensitivity analysis, although there is no common subject across the two Phase 3 trials; this reviewer conducted a sensitivity analysis by excluding the 35 subjects. Even after excluding all 35 common subjects, Topicort (desoximetasone) spray, 0.25% was still statistically superior to vehicle spray in two studies (DSXS-0808 and DSXS-0914) in the treatment of moderate to severe plaque psoriasis. Furthermore, this reviewer evaluated the efficacy of the 35 subjects where 33 of the 35 subjects were common across DSXS-0906 (Phase 2) and DSXS-0808 (Phase 3), and 2 subjects were common across DSXS-0906 (Phase 2) and DSXS-0914 (Phase 3). For Study DSXS-0808, the Clinical Success for the desoximetasone spray arm and vehicle arm were 7/20 (35%), and 0%, respectively. For Study DSXS-0914, there was 1 subject in each arm, and the subject in the desoximetasone spray arm was a Clinical Success while the subject in the vehicle arm was not. The results from this sensitivity analysis are presented in the Appendix.

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 eCTD format and was entirely electronic. The datasets in this review are archived at the following locations: \\Cdsesub5\evsprod\NDA204141\\0000\m5\datasets\dsxs-0808\analysis\ \\Cdsesub5\evsprod\NDA204141\\0000\m5\datasets\dsxs-0914\analysis\.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor submitted electronic analysis datasets for review. The primary efficacy analyses could be conducted using the submitted analysis datasets (adxe.xpt, adsl.xpt).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

According to the final protocol, the primary objective of the trials was to evaluate the efficacy and safety of Topicort (desoximetasone) 0.25% topical spray compared to a vehicle spray in patients with moderate to severe plaque psoriasis.

Each Phase 3 trial enrolled a total of 120 subjects from 9 centers (10 were approved by the IRB, but only 9 of them enrolled subjects as stated on page 6 of the respective study reports) and subjects were male or female at least 18 years of age with a "definite clinical diagnosis of stable plaque psoriasis" involving ≥10% body surface area (BSA), a combined total lesion severity score (TLSS) of ≥7, a plaque elevation score of ≥3 of the target lesion, and a Physician Global Assessment (PGA) of 3 or 4 at baseline were enrolled. According to the protocol, the target lesion for each subject was to be at least 5 cm^2 in area with plaque elevation score of at least 3 and total lesion severity score (TLSS) of at least 7. The target lesion must not be on the face, genitals, or intertriginuous area (i.e., breast fold, gluteal crease, axilla, etc.). According to the Integrated Summary of Efficacy (ISE, page 12), the lesion that was the most severe was selected as the target lesion.

Subjects were instructed to spray the study medication directly to all affected areas, and rub in gently, and completely twice a day (morning and evening approximately 12 hours apart) for 28 days. Subjects returned to the clinic for assessment of signs and symptoms of psoriasis, adverse events at Days 7, 14, and 28.

Subjects were randomized in a 1:1 ratio to one of the following two groups:

- Topicort (desoximetasone) Spray, 0.25%
- Vehicle spray

According to the protocol, subjects were randomized in blocks of 2; however, the randomization was not stratified by study centers.

The protocol-specified co-primary efficacy endpoints are:

- Proportion of subjects who are considered a Clinical Success (PGA score of 0 or 1) at Day 28.
- proportion of subjects who are considered a Treatment Success for the Target Lesion (a score of 0 or 1 for each of the three signs (i.e., erythema, scaling and plaque elevation) at Day 28

The protocol-specified secondary endpoints are:

- mean change from baseline in TLSS at Day 28
- mean change from baseline in PGA score at Day 28
- mean change from baseline in %BSA affected at Day 28

3.2.2 Statistical Methodologies

The efficacy analysis was based on the Intent to Treat (ITT) population. The definitions of ITT as well as Per Protocol (PP) analysis set were not provided in the protocol; however, for the ITT, based on the study report, the sponsor appears to have included all randomized subjects who used the study medication, with at least one post-baseline assessment (page 9 of study report).

For handling of missing data, the last observation carried forward (LOCF) was used as the primary imputation method. At the Pre-NDA meeting, the Agency commented that the "LOCF might not be scientifically justified". As a sensitivity analysis, per the Agency's comments provided at the Pre-NDA meeting, the sponsor considered the Generalized Estimating Equations (GEE) method which model included "fixed effects for study number, visit number, pooled treatment group, and the interaction between visit number and pooled treatment group"; however, the sponsor stated that the model failed to converge (ISE, page 40).

For the analysis of co-primary efficacy endpoints, the protocol-specified method was to use a two-sided continuity corrected Z-test. Per the Agency's comments at the Pre-NDA meeting, as a sensitivity analysis, the sponsor also considered Cochran-Mantel-Haenszel test stratified by center, which results were included in the ISE section (page 42); however, it should be noted that because the randomization was not stratified by center, the results from such analysis would not be meaningful. For the secondary endpoints, the protocol-specified method is to use the Analysis of Variance.

According to the protocol, a "hierarchical evaluation of the two secondary endpoints which deal with disease severity (i.e. change from baseline for PGA and for TLSS) will be used to conserve the type I error rate at 0.05". The protocol stated that the first evaluation will be for the change from baseline in TLSS, using a two-sided, $\alpha = 0.05$ level of significance. If superiority of the test product over its vehicle is demonstrated ($p<0.05$) then the PGA change from baseline values will be examined. This evaluation will be conducted at a two-sided, $\alpha = 0.05$ level of significance. Then the protocol stated that "the %BSA affected is a measure of the extent of disease coverage

and is independent from, and uses different observations (i.e. unique data) than, the two endpoints that deal with disease severity. The evaluation of the change from baseline in %BSA will be at a two-sided, $\alpha = 0.05$ level of significance, as no multiplicity issues exist between this endpoint and any other secondary endpoint". It should be noted that from a statistical perspective, the sponsor's proposed statistical analysis plan for the secondary endpoints does not adjust for multiplicity.

The protocol stated that "success for the primary endpoints requires that for both of the dichotomous endpoints, the proportion of patients considered a success in the test treatment group is shown to be statistically ($p<0.05$) greater than the proportion of patients considered a success in the vehicle treatment group".

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study DSXS-0808 enrolled 119 subjects (59 Desoximetasone, 0.25% spray, 60 vehicle), and Study DSXS-0914 enrolled 120 subjects (60 Desoximetasone, 0.25% spray, 60 vehicle). For both studies, the discontinuation rate for vehicle subjects (11%) was higher than for Desoximetasone, 0.25% spray subjects (9%). The reasons for discontinuation are presented in the table below.

Table 5. Subject Disposition

	DSXS-0808		**DSXS-0914**	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
Enrolled subjects	60	60	60	60
ITT [(1)] Subjects	59	60	60	60
Completed	55	54	54	53
Reason for Discontinuation	5 (8.5%)	6 (10%)	6 (10%)	7 (11.7%)
Adverse Event	1	2	0	2
Lost to follow-up	1	1	1	0
Insufficient response	1	1	1	0
Withdrew consent	0	2	1	1
Enrolled in error	0	0	0	1
Other	2	0	3	3

Source: sponsor's study report
(1) The sponsor's definition of ITT is not explicitly defined in the protocol; however, it appears from page 9 of the study report, the sponsor defined ITT as all randomized subjects who had at least one post-baseline assessment.

Both studies were fairly evenly balanced across treatment arms in terms of age, however, in both studies, more male subjects than female subjects were enrolled. Most subjects were white in both studies.

Table 6. Demographics

	DSXS-0808		DSXS-0914	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT [(1)] Subjects	59	60	60	60
Age				
<65	50 (83.3%)	43 (71.7%)	51 (85.0%)	44 (77.3%)
≥65	9 (16.7%)	17 (28.3%)	9 (15.0%)	16 (22.7%)
Sex				
Female	17 (28.8%)	17 (28.3%)	23 (38.3%)	25 (41.7%)
Male	42 (71.2%)	43 (71.7%)	37 (61.7%)	35 (58.3%)
Race				
White	57 (96.6%)	57 (95.0%)	57 (95.0%)	56 (93.3%)
Black	2 (3.9%)	2 (3.3%)	2 (2.3%)	0
Asian	0	1 (1.7%)	0	2 (3.3%)
Other	0	0	1 (1.7%)	2 (3.3%)

Source: sponsor's table 6 (study report)

At baseline, about 70% of the subjects were graded as "moderate" on the PGA scale (i.e., PGA=3) with the mean percentage of BSA affected of about 16. Table 7 below shows the baseline disease severity for the two studies.

Table 7. Baseline disease severity

	DSXS-0808		DSXS-0914	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT [(1)] Subjects	59	60	60	60
Baseline %BSA affected				
mean±SD	15.6±9.1	16.0±10.4	17.8±14.3	15.7±9.4
range	10-60	10-70	10-86	10-70
Baseline PGA				
PGA=3 (moderate)	44 (74.6%)	44 (73.3%)	38 (63.3%)	40 (66.7%)
PGA=4 (severe)	15 (25.4%)	16 (26.7%)	22 (36.7%)	19 (31.7%)
PGA=5 (very severe)	-	-	-	1 (1.7%)
Baseline TLSS				
mean±SD	9.5±1.5	9.4±1.2	10.0±1.6	10.0±1.6
range	7-15	7-12	7-14	7-15
Baseline target lesion size				
mean±SD	41.5±39.5	38.02±33.1	50.3±100.7	57.4±87.4
range	6-209	5-196	6-651	6-565

Source: reviewer's table

3.2.4 Results and Conclusions

According to the sponsor's analysis of the primary efficacy analysis results, both Phase 3 trials (DSXS-0808 and DSXS-0914) met the statistical significance level of 0.05.

Table 8. Sponsor's Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	**Vehicle**	**p-value[(3)]**
Study 0808			
Clinical Success [(1)]	18/59 (30.5%)	3/60 (5.0%)	0.0003
Treatment Success [(2)]	23/59 (39.0%)	4/60 (6.7%)	<0.0001
Study 0914			
Clinical Success [(1)]	32/60 (53.3%)	11/60 (18.3%)	<0.0001
Treatment Success [(2)]	32/60 (53.3%)	10/60 (16.7%)	<0.0001

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
(3) P-value is calculated from two-sided continuity corrected Z test.
Source: sponsor's analysis.

As a sensitivity analysis, this reviewer considered the worst case scenario and imputed the missing data in the vehicle arm as successes, and the missing data in the desoximetasone arm as

failures. Even under such worst case scenario, both Phase 3 trials (DSXS-0808 and DSXS-0914) met the statistical significance level of 0.05 for the co-primary endpoints.

Table 9. Sensitivity Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	Vehicle	p-value
Study 0808			
Clinical Success [(1)]	18/59 (30.5%)	9/60 (15.0%)	0.0434
Treatment Success [(2)]	27/59 (45.8%)	9/60 (15.0%)	0.0003
Study 0914			
Clinical Success [(1)]	31/60 (51.7%)	17/60 (28.3%)	0.0091
Treatment Success [(2)]	32/60 (53.3%)	17/60 (28.3%)	0.0053

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
P-value is calculated from Chi-square test.
Source: reviewer's analysis.

Table 10 provides the analysis results for the secondary endpoints based on the ITT population. It should be noted that the sponsor's proposed label does not include the results of the secondary endpoints.

Table 10. Sponsor's Analysis Results of the Secondary Efficacy Endpoints

	Desoximetasone, 0.25% spray Mean±SD	Vehicle Mean±SD	p-value[(1)]
Study 0808	N=59	N=60	
Mean change from baseline in TLSS	4.73±3.08	1.93±1.96	<0.0001
Mean change from baseline in PGA	1.14±0.90	0.50±0.68	<0.0001
Mean change from baseline in %BSA affected	2.24±3.79	0.37±2.05	0.0011
Study 0914			
Mean change from baseline in TLSS	6.18±3.13	3.02±2.97	<0.0001
Mean change from baseline in PGA	1.73±1.06	0.85±0.94	<0.0001
Mean change from baseline in %BSA affected	3.47±4.74	1.27±4.23	0.0083

(1) P-value is calculated from CMH test stratified by sites.
Source: reviewer analysis.

3.3 Evaluation of Safety

The summaries of adverse events (AEs) are presented in Table 11 for DSXS-808, and in Table 12 for DSXS-0914.

Table 11. Summary of Adverse Events for DSXS-0808

	Study 0808	
	Desoximetasone, 0.25% spray N=59	**Vehicle N=60**
Application site dryness	4 (6.7%)	5 (8.3%)
Application site erythema	-	2 (3.3%)
Application site irritation	-	2(3.3%)
Application site pruritus	3 (5.0%)	5 (8.3%)
Arthralgia	2 (3.3%)	1 (1.7%)
Diarrhea	2 (3.3%)	1 (1.7%)
Headache	3 (5.0%)	1 (1.7%)
Hypertension	2 (3.3%)	-
Musculoskeletal Pain	2 (3.3%)	1 (1.7%)
Pain in extremity	2 (3.3%)	-
Sinus headache	-	2 (3.3%)

Source: sponsor's table 10 (page 48 of 52 in Study 808 Study Report)

Table 12. Summary of Adverse Events for DSXS-0914

	Study 0914	
	Desoximetasone, 0.25% spray N=60	**Vehicle N=60**
Application site dryness	-	1 (1.7%)
Application site irritation	4 (6.7%)	3 (5.0%)
Application site pain	-	2(3.3%)
Hypertension	-	1 (1.7%)
Nasopharyngitis	-	1 (1.7%)

Source: sponsor's submission. Appendix 16.2.7.3

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

It appears that there is no differential treatment effect by gender or age, although the proportion of subjects with clinical success appears to be higher for those >65 years of age, it should be noted that the majority of the subjects were ≤65 years of age. For the efficacy by race, 95% of the subjects were white in the two Phase 3 trials. Table 13 shows the proportion of subjects with clinical success at Day 28 by age, gender and race.

Table 13. Proportion of Subjects with Clinical Success at Day 28 by Gender, Race and Age

	DSXS-0808		DSXS-0914	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT (1) Subjects	59	60	60	60
Age				
18-65	14/50 (28.0%)	1/44 (2.3%)	26/52 (50.0%)	8/45 (17.8%)
>65	4/9 (44.4%)	2/16 (12.5%)	6/8 (75.0%)	3/15 (20.0%)
Sex				
Female	6/17 (35.3%)	1/17 (5.9%)	10/23 (43.5%)	4/25 (16.0%)
Male	12/42 (28.6%)	2/43 (4.7%)	22/37 (59.5%)	7/35 (20.0%)
Race				
Asian	-	0/1 (0%)	-	0/2 (0%)
Black	1/2 (50%)	0/2 (0%)	1/2 (50%)	-
White	17/57 (29.8%)	3/57 (5.3%)	30/57 (52.6%)	11/56 (19.6%)
Native American	-	-	-	0/1 (0%)
Other Pacific	-	-	1/1 (100%)	0/1 (0%)

(1) The sponsor's definition of ITT is not explicitly defined in the protocol; however, it appears from page 9 of the study report, the sponsor defined ITT as all randomized subjects who had at least one post-baseline assessment.
Source: reviewer's analysis

Table 14 shows the proportion of subjects with treatment success at Day 28 by age, gender and race.

Table 14. Proportion of Subjects with Treatment Success at Day 28 by Gender, Race and Age

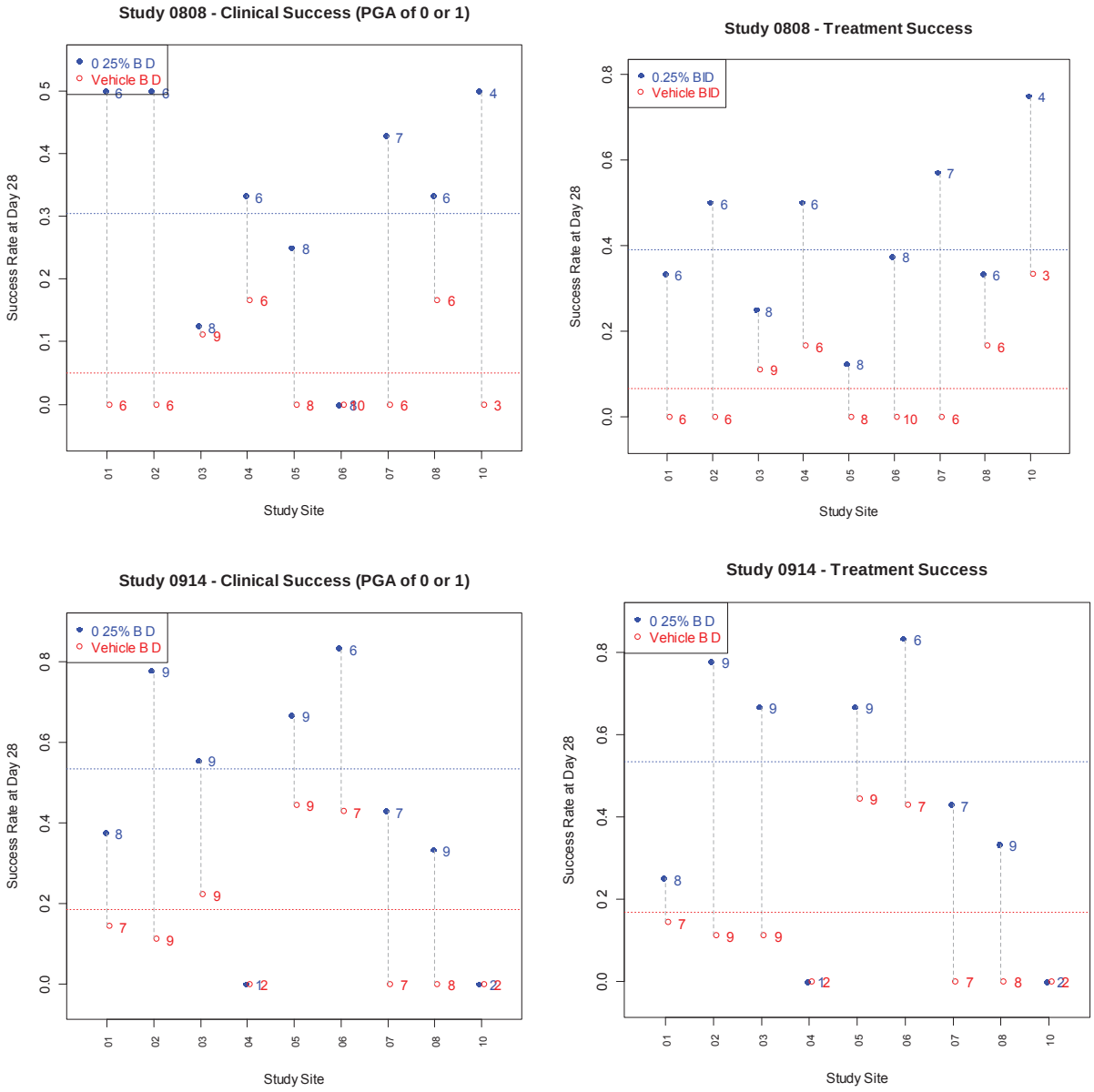
	DSXS-0808		DSXS-0914	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT (1) Subjects	59	60	60	60
Age				
18-65	18/50 (36.0%)	2/44 (4.6%)	26/52 (50.0%)	7/45 (15.6%)
>65	5/9 (55.6%)	2/16 (12.5%)	6/8 (75.0%)	3/15 (20.0%)
Sex				
Female	8/17 (47.1%)	1/17 (5.9%)	10/23 (43.5%)	3/25 (12.0%)
Male	15/42 (35.7%)	3/43 (7.0%)	22/37 (59.5%)	7/35 (20.0%)
Race				
Asian	-	0/1 (0%)	-	0/2 (0%)
Black	1/2 (50%)	0/2 (0%)	1/2 (50%)	-
White	22/57 (38.6%)	4/57 (7.0%)	30/57 (52.6%)	10/56 (17.9%)
Native American	-	-	-	0/1 (0%)
Other Pacific	-	-	1/1 (100%)	0/1 (0%)

(1) The sponsor's definition of ITT is not explicitly defined in the protocol; however, it appears from page 9 of the study report, the sponsor defined ITT as all randomized subjects who had at least one post-baseline assessment.
Source: reviewer's analysis

4.2 Efficacy by Center

The efficacy results appear to be consistent across the pooled study sites and the efficacy by center plots are presented in Figure 1. The Breslow-Day test was not statistically significant (for Study 0808, the p-values were 0.5128 and 0.7836 for the Clinical Success and Treatment Success endpoints, respectively, and for Study 0914, the p-values were 0.6742 and 0.5418 for the Clinical Success and Treatment Success endpoints, respectively).

Figure 1. Efficacy by Center Plots



Source: reviewer's plots

4.3 Efficacy by baseline disease severity

In this submission, the co-primary endpoints involve both the overall disease as well as disease of the target lesion. As such, this reviewer evaluated the efficacy by its corresponding baseline disease severity.

In Table 15, the Clinical Success by baseline percentage of BSA and also by baseline PGA scores is provided. Subjects were categorized into three groups: %BSA=10, 11≤%BSA≤15, or %BSA≥16. The categories were created so as to have enough subjects in each category.

Subjects with 10-15 %BSA affected had higher Clinical Success rates than those with ≥16 %BSA at baseline.

In terms of the baseline PGA score, about 70% of the subjects who entered the trial had a baseline PGA score of 3 (moderate), and the treatment effect for the Clinical Success is about 30% for these subjects in both trials. For the subjects who entered the trial with a PGA of 4 (severe), while DSXS-0808 showed that the treatment effect is only about 13.3%, results from DSXS-0914 show that the treatment effect for the Clinical Success is about 45%. However, the number of subjects in this severity group is relatively small to draw any reasonable inference.

Table 15. Clinical Success by baseline %BSA and baseline PGA score

	DSXS-0808		**DSXS-0914**	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT (1) Subjects	59	60	60	60
Baseline %BSA				
10	8/21 (38.1%)	1/16 (6.3%)	7/14 (50%)	2/14 (14.3%)
11-15	7/21 (33.3%)	2/29 (6.9%)	20/28 (71.4%)	8/29 (27.6%)
≥16	3/17 (17.6%)	0/15 (0%)	5/18 (27.8%)	1/17 (5.9%)
Baseline PGA				
PGA=3 (moderate)	16/44 (36.4%)	3/44 (6.8%)	21/38 (55.3%)	10/40 (25.0%)
PGA=4 (severe)	2/15 (13.3%)	0/16 (0%)	11/22 (50.0%)	1/19 (5.3%)
PGA=5 (very severe)	-	-	-	0/1 (0%)

(1) The sponsor's definition of ITT is not explicitly defined in the protocol; however, it appears from page 9 of the study report, the sponsor defined ITT as all randomized subjects who had at least one post-baseline assessment.
Source: reviewer's analysis

The Treatment Success by baseline disease severity of the target lesion (i.e., erythema, scaling, plaque elevation as well as TLSS) is shown in Table 16. The target lesions of most subjects who entered the trials had moderate erythema, moderate scaling, moderate plaque elevation. Because the number of subjects in other severity groups is too small, it is difficult to draw any reasonable inference. For the TLSS, those subjects with scores of 7-9 had higher Treatment Success compared to those with scores of 10-15.

Table 16. Treatment Success by baseline disease severity of the target lesion

	DSXS-0808		DSXS-0914	
	Desoximetasone, 0.25% spray	**Vehicle**	**Desoximetasone, 0.25% spray**	**Vehicle**
ITT [(1)] Subjects	59	60	60	60
Erythema				
1=almost clear	0/1 (0%)	-	-	-
2=mild	4/5 (80%)	0/10 (0%)	3/5 (60%)	1/2 (50%)
3=moderate	17/43 (39.5%)	4/41 (9.8%)	21/36 (58.3%)	9/37 (24.3%)
4=severe	1/9 (11.1%)	0/9 (0%)	8/17 (47.1%)	0/19 (0%)
5=very severe	1/1 (100%)	-	0/2 (0%)	0/2 (0%)
Scaling				
1=almost clear	-	0/1 (0%)	-	-
2=mild	2/8 (25%)	2/4 (50%)	2/5 (40%)	0/3 (0%)
3=moderate	17/35 (48.6%)	2/37 (5.4%)	18/32 (56.3%)	9/36 (25%)
4=severe	3/13 (23.1%)	0/18 (0%)	10/19 (52.6%)	1/19 (5.3%)
5=very severe	1/3 (33.3%)	-	2/4 (50%)	0/2 (0%)
Plaque elevation				
2=mild	-	-	-	0/1 (0%)
3=moderate	20/45 (44.4%)	4/51 (7.8%)	21/37 (56.8%)	9/38 (23.7%)
4=marked	2/12 (16.7%)	0/8 (0%)	10/22 (45.5%)	1/20 (5%)
5=severe	1/2 (50%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
TLSS				
7-9	19/37 (51.4%)	4/39 (10.3%)	17/29 (58.6%)	9/31 (29.0%)
10-15	4/22 (18.2%)	0/21 (0%)	15/31 (48.4%)	1/29 (3.4%)

(1) The sponsor's definition of ITT is not explicitly defined in the protocol; however, it appears from page 9 of the study report, the sponsor defined ITT as all randomized subjects who had at least one post-baseline assessment.
Source: reviewer's analysis

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues affecting the overall conclusion. While there were 35 common subjects across the Phase 2 trial and the Phase 3 trials, there were no common subjects across the two Phase 3 trials, and with sufficient time between the Phase 2 and Phase 3 trials for the common subjects, consequently, the two trials may be considered as two independent Phase 3 trials.

5.2 Collective Evidence

The sponsor submitted results of two Phase 3 trials to support the efficacy claim for plaque psoriasis. Desoximetasone spray, 0.25% was statistically superior to vehicle spray in two studies (Studies 0808 and 0914) in the treatment of moderate to severe plaque psoriasis. The protocol-specified co-primary efficacy endpoints were the following:

- proportion of subjects who were a Clinical Success (PGA score of 0 or 1) at Day 28
- proportion of subjects who were a Treatment Success for the Target Lesion (a score of 0 or 1 for each of the three signs, i.e., erythema, scaling and plaque elevation) at Day 28.

Summary of co-primary efficacy results is given in the following table.

Table 17. Sponsor's Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	Vehicle	p-value
Study 0808			
Clinical Success [(1)]	18/59 (30.5%)	3/60 (5.0%)	0.0003
Treatment Success [(2)]	23/59 (39.0%)	4/60 (6.7%)	<0.0001
Study 0914			
Clinical Success [(1)]	32/60 (53.3%)	11/60 (18.3%)	<0.0001
Treatment Success [(2)]	32/60 (53.3%)	10/60 (16.7%)	<0.0001

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
P-value is calculated from two-sided continuity corrected Z test.
Source: sponsor's analysis.

5.3 Conclusions and Recommendations

Efficacy findings from the two Phase 3 trials (Studies 0808 and 0914) established that desoximetasone topical spray, 0.25% was superior to vehicle in the treatment of moderate to severe plaque psoriasis after 28 days of treatment.

APPENDIX

It should be noted that in the Pre-NDA meeting submission (meeting date: 7/20/2011), the sponsor stated that there are 35 common subjects across the Phase 2 and Phase 3 trials. According to the submitted datasets, 33 of the 35 subjects were common across DSXS-0906 (Phase 2) and DSXS-0808 (Phase 3) trials, and 2 subjects were common across DSXS-0906 (Phase 2) and DSXS-0914 (Phase 3) trials. Even after excluding all 35 common subjects, desoximetasone spray, 0.25% was still statistically superior to vehicle spray in two studies (DSXS-0808 and DSXS-0914) in the treatment of moderate to severe plaque psoriasis. The results from this sensitivity analysis are shown below.

Table 18. Reviewer's Sensitivity Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	**Vehicle**	**p-value**
DSXS-0808			
Clinical Success (1)	11/39 (28.2%)	3/47 (6.4%)	0.02
Treatment Success (2)	16/39 (41.0%)	4/47 (8.5%)	0.001
DSXS-0914			
Clinical Success (1)	31/59 (52.6%)	11/59 (18.7%)	<0.0001
Treatment Success (2)	31/59 (52.6%)	10/59 (16.9%)	<0.0001

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
P-value is calculated from CMH test stratified by sites.
Source: reviewer's analysis – excluded the common subjects (i.e., 33 subjects in Study 0808 and 2 subjects in Study 0914)

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/s/

CARIN J KIM
01/16/2013

MOHAMED A ALOSH
01/16/2013

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

STATISTICAL REVIEW AND EVALUATION

ADDENDUM

NDA/BLA #:	NDA 204141
Supplement #:	Original-1
Drug Name:	Desoximetasone Spray, 0.25%
Indication(s):	Plaque psoriasis
Applicant:	Taro Pharmaceuticals
Date(s):	Stamp date: 6/12/2012 PDUFA: 4/12/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Carin Kim, Ph.D.
Concurring Reviewers:	Mohamed Alosh, Ph.D.
Medical Division:	Division of Dermatologic and Dental Products
Clinical Team:	Melinda McCord, MD Gordana Diglisic, MD
Project Manager:	J Paul Phillips

Keywords: Clinical studies, Superiority trials

Statistical review for NDA 204141 was signed off in DARRTS on 1/16/2013. However, there was a typographical error in Table 9 (page 12) where the number of Treatment Success and its success rate (%) for the Desoximetasone, 0.25% spray in Study 0808 should be 23 and 39.0%, respectively. The following table should replace the Table 9 in the review.

Table 9. Sensitivity Analysis Results of the Co-primary Efficacy Endpoints

	Desoximetasone, 0.25% spray	**Vehicle**	**p-value**[3]
Study 0808			
Clinical Success [1]	18/59 (30.5%)	9/60 (15.0%)	0.043
Treatment Success [2]	23/59 (39.0%)	9/60 (15.0%)	0.003
Study 0914			
Clinical Success [1]	31/60 (51.7%)	17/60 (28.3%)	0.009
Treatment Success [2]	32/60 (53.3%)	17/60 (28.3%)	0.005

(1) Clinical success is defined as having PGA of 0 or 1 at Day 28
(2) Treatment success is defined as having signs and symptoms of score 0 or 1.
(3) P-value is calculated from Chi-square test.
Source: reviewer's analysis.

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/s/

CARIN J KIM
02/12/2013

MOHAMED A ALOSH
02/12/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204141 **Applicant: Taro** **Stamp Date: 6/12/2012**

Drug Name: Topicort
(desoximetasone spray, 0.25%)

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

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary 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 (if applicable).		X		Efficacy by gender, racial and geriatric subgroups can be done using the submitted data sets.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _Yes_

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

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

Comments to be forwarded to the Applicant for the 74-day letter:

- According to the submission, the randomization (with a block size of 2) was performed using a computer-generated randomization scheme. It is not clear from the submission whether randomization was stratified by center, and consequently, whether stratification of the statistical analysis by center would be meaningful. The sponsor should submit details of the randomization scheme and whether any stratification factors were considered for the randomization.

Carin Kim	7/17/2012
Statistical Reviewer	Date
Supervisor/Team Leader	Date

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/s/

CARIN J KIM
07/20/2012

MOHAMED A ALOSH
07/23/2012