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 #:	207589
Drug Name:	Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%
Indication(s):	Plaque Psoriasis
Applicant:	LEO Pharma A/S
Date(s):	Letter Date: 12/18/2014
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Review Priority:	Standard
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Keywords: psoriasis, combination product

Table of Contents

1 EXECUTIVE SUMMARY

LEO Pharma A/S is developing Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% for the treatment of plaque psoriasis. The active ingredients of calcipotriene and betamethasone dipropionate (BDP) are the same active ingredients, in the same concentrations, as the following approved products:

- Taclonex® Ointment (NDA 021852): approved on January 9, 2006 for the indication of topical treatment of plaque psoriasis in adults 18 years of age and older for up to four weeks.
- Taclonex® Topical Suspension (NDA 022185):
    - Approved on May 9, 2008 for the treatment of psoriasis vulgaris of the scalp in adults 18 years and older.
    - Supplement approved on October 17, 2012 to extend the indication to include psoriasis vulgaris of the body.

To establish the safety and efficacy of Enstilar® foam, the applicant submitted data from one Phase 3 trial (Study 1001) and two Phase 2 trials (Study 7 and Study 35). The applicant designated Studies 7 and 1001 as pivotal/confirmatory trials and Study 35 as a supportive trial. Study 7 compared Enstilar® foam to the two monads (no vehicle arm) and Study 1001 compared Enstilar® foam to vehicle foam (no monad arms). Study 35 compared Enstilar® foam to Taclonex® ointment, vehicle foam and vehicle ointment. The inclusion and exclusion criteria were similar among the studies. Subjects must have had an Investigator Global Assessment (IGA) score of at least mild, involving 2-30% body surface area (BSA) at baseline. It should be noted that the requirement of 2-30% BSA in Study 1001 and Study 35 included only trunk and limbs whereas in Study 7 also included the scalp.

The protocol-specified primary efficacy endpoint was the proportion of subjects with 'treatment success' at Week 4, where treatment success is defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. Table 1 presents the primary efficacy results for Studies 7 and 1001. In Study 7, Enstilar® foam was statistically superior to both the BDP foam monad ($p = 0.047$) and the calcipotriene foam monad ($p < 0.001$). In Study 1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$). The results for Study 35 are presented in Table A.1 in the Appendix and are supportive of those observed in Studies 7 and 1001.

Table 1: Primary Efficacy Results at Week 4 (ITT, LOCF, MI)

	Enstilar® Foam	**Betamethasone dipropionate in Vehicle Foam**	**Calcipotriene in Vehicle Foam**	**Vehicle Foam**
Study 7	(N=100)	(N=101)	(N=101)	-
Treatment Success Rate	45 (45.0%)	31 (30.7%)	15 (14.9%)	-
P-value	-	0.047	<0.001	-
Study 1001	(N=323)	-	-	(N=103)
Treatment Success Rate	172.1 (53.3%)	-	-	4.9 (4.8%)
P-value	-	-	-	<0.001

Source: Reviewer's Analysis

For Study 1001, the applicant reported that a center (US15; Dr. Jane Lee) did not perform assessments as specified in the protocol. Specifically, the applicant stated the following:

> "One site (Site US15) confirmed by signature of a protocol deviation that they could not confirm that the scores given for the m-PASI assessments conformed to the directions specified in the consolidated clinical study protocol. It was identified that the errors in clinical judgment were isolated to the extent calculation in the m-PASI transformation and were not implicated in any other investigator assessments. The site recruited several subjects and hence completed multiple randomisation blocks. Any effect was therefore expected to be balanced between LEO 90100 and the vehicle group with a limited impact on the results of the trial."

The Agency conducted an inspection of this center to verify the above protocol violations and to determine whether other assessments (e.g., IGA) were done according to the protocol. The Agency determined that the investigator at this center did not properly assess the extent of psoriatic involvement of the arms, trunk, and legs for the calculation of m-PASI. While the Agency was able to confirm that the IGA assessments were done according to protocol, this reviewer conducted a sensitivity analysis where all subjects from this center were removed. Table 2 presents the primary efficacy results at Week 4 with and without center #15. The treatment success rates are very similar with and without center #15, and the center did not affect the overall conclusion.

Table 2: Primary Efficacy Results at Week 4 With and Without Center #15 in Study 1001 (ITT, MI)

	Enstilar® Foam	**Vehicle Foam**
With Center #15	(N=323)	(N=103)
Treatment Success Rate	172.1 (53.3%)	4.9 (4.8%)
P-value	-	<0.001
Without Center #15	(N=303)	(N=97)
Treatment Success Rate	160.5 (53.0%)	4.9 (5.0%)
P-value	-	<0.001

Source: Reviewer's Analysis

2 INTRODUCTION

2.1 Overview

LEO Pharma A/S is developing Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% for the treatment of plaque psoriasis. The active ingredients of calcipotriene and betamethasone dipropionate (BDP) are the same active ingredients, in the same concentrations, as the following approved products:

- Taclonex® Ointment (NDA 021852): approved on January 9, 2006 for the indication of topical treatment of plaque psoriasis in adults 18 years of age and older for up to four weeks.
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    - Approved on May 9, 2008 for the treatment of psoriasis vulgaris of the scalp in adults 18 years and older.
    - Supplement approved on October 17, 2012 to extend the indication to include psoriasis vulgaris of the body.

2.1.1 Regulatory History

On March 7, 2012, the applicant and the Agency met for a Pre-IND meeting. For that meeting, the applicant submitted draft protocols for the following Phase 2 trials:

- Study 7: 3-arm trial to compare the safety and efficacy of Enstilar® foam to the monads (calcipotriene 0.005% and betamethasone dipropionate 0.064%) for the treatment of both scalp and body psoriasis.
- Study 35: 4-arm trial to compare the safety and efficacy of Enstilar® foam, vehicle foam, Taclonex® Ointment, and ointment vehicle in subjects with body psoriasis.

The applicant asked whether the above two Phase 2 trials and a single Phase 3 trial that does not contain the monad arms (i.e., only Enstilar® foam and vehicle foam) would be sufficient for a NDA application. The Agency stated that the contribution of the monads could be demonstrated in an appropriately designed Phase 2 trial, which could lead to a Phase 3 clinical trial without monad arms. In addition, the Agency stated that if the applicant is seeking an approval for both body and scalp psoriasis, then clinical trials should be designed to demonstrate the safety and efficacy of the proposed product in each indication.

An End-of-Phase 2 (EOP2) meeting was scheduled for May 15, 2013; however, the applicant cancelled the meeting after receiving the Agency's pre-meeting communication. The meeting package contained the results of Studies 7 and 35, and included a protocol for a Phase 3 trial (Study 1001). The proposed Phase 3 trial would investigate the safety and efficacy of Enstilar® foam to vehicle foam for the treatment of psoriasis on the body. In the pre-meeting communication, the Agency agreed with the applicant that the two Phase 2 trials and the proposed Phase 3 trial would be acceptable for a NDA. The Agency also agreed with the proposed primary efficacy endpoint of the proportion of subject with 'treatment success' at Week 4, where treatment success is defined as an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. In addition, the Agency commented on the analysis method for the primary endpoint, the evaluation of tertiary endpoints, randomization, and the handling of missing data.

On May 22, 2013, the applicant submitted responses to the Agency's written EOP2 comments. An amended Phase 3 protocol based on these responses was submitted on May 31, 2013. An advice letter regarding these two submissions was sent to the applicant on August 30, 2013.

On March 17, 2014, the Agency and the applicant met for a Pre-NDA meeting. The Agency provided general comments regarding the Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and data submission.

2.1.2 Clinical Studies Overview

The applicant submitted data from one Phase 3 trial (Study 1001) and two Phase 2 trials (Study 7 and Study 35), see Table 3. The inclusion and exclusion criteria were similar among the studies. Subjects must have had an IGA score of at least mild, involving 2-30% BSA at baseline. It should be noted that the requirement of 2-30% BSA in Study 1001 and Study 35 included only trunk and limbs whereas in Study 7 also included the scalp. The main body of this review focuses on the pivotal/confirmatory studies (Studies 7 and 1001), while the supportive study (Study 35) is briefly summarized in the Appendix.

Table 3: Clinical Study Overview

Study	Study Population	Treatment Arms	Number of Subjects	Dates
LP0053-1001 Phase 3 (Pivotal) 27 sites in US	Psoriasis vulgaris (body), IGA ≥ 2, 2-30% BSA, m-PASI ≥ 2 (body)	Enstilar® Foam	323	6/13/2013 – 10/2/2013
		Vehicle Foam	103	
LEO 90100-7 Phase 2 (Pivotal) 28 sites in US	Psoriasis vulgaris (body and scalp), IGA ≥ 2, 2-30% BSA, ≥10% of the scalp affected, m-PASI ≥ 2 (body)	Enstilar® Foam	100	5/7/2012 – 10/10/2012
		Betamethasone dipropionate in Vehicle Foam	101	
		Calcipotriene in Vehicle Foam	101	
LEO 90100-35 Phase 2 (Supportive) 35 sites in US	Psoriasis vulgaris (body), IGA ≥ 2, 2-30% BSA, m-PASI ≥ 2 (body)	Enstilar® Foam	141	5/10/2012 – 9/19/2012
		Taclonex® Ointment	135	
		Vehicle Foam	49	
		Vehicle Ointment	51	

2.2 Data Sources

This reviewer evaluated the applicant's clinical study reports, datasets, clinical summaries, and proposed labeling. This submission was submitted in eCTD format and entirely electronic. The datasets in this review are archived at the following location:
\\cdsesub1\evsprod\NDA207589\0000\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The databases for the studies required minimal data management prior to performing analyses and no request for additional datasets were made to the applicant.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study 7 was a multicenter, double-blind, randomized, parallel-group, active-controlled, Phase 2 trial conducted in the United States. For enrollment, subjects must have had plaque psoriasis on the body (trunk and/or limbs) involving 2-30% total body surface area (BSA), plaque psoriasis on the scalp involving and at least 10% of the total scalp area, a modified Psoriasis Area and Severity Index (m-PASI) score ≥ 2 and an IGA score of at least mild for both scalp and body. Subjects were randomized in a 1:1:1 ratio to one of the following treatment arms: Enstilar® foam, betamethasone dipropionate (BDP) in vehicle foam, and calcipotriene in vehicle foam. The randomization was stratified by baseline disease severity (IGA=2 or IGA≥3). Subjects applied study product once daily for 4 weeks. Subjects were evaluated at baseline and Weeks 1, 2, and 4.

Study 1001 was a multicenter, randomized, double-blind, parallel-group, vehicle-controlled, Phase 3 trial conducted in the United States. For enrollment, subjects must have had plaque psoriasis on the body (trunk and/or limbs) involving 2-30% BSA, m-PASI score ≥ 2 and an IGA score of at least mild for the body. Subjects were randomized in a 3:1 ratio to either Enstilar® foam or vehicle foam. The randomization was stratified by center. Subjects applied study product once daily for 4 weeks. Subjects were evaluated at baseline and Weeks 1, 2, and 4.

The protocol-specified primary efficacy endpoint in both studies was the proportion of subjects with 'treatment success' on the trunk and limbs at Week 4. Treatment success was defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline.

The protocol-specified secondary efficacy endpoints were different between the two studies. The protocol for Study 7 specified one secondary endpoint, i.e., the proportion of subject with treatment success on the trunk and limbs at Week 1. For Study 1001, the protocol specified two secondary endpoints: m-PASI at Week 1 and m-PASI at Week 4. Since the secondary endpoints were different and the applicant is not seeking labeling claims for any of the secondary endpoints, this review will not present the results of the secondary endpoints.

Table 4: Investigator's Global Assessment (IGA) scale

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	Almost Clear	Plaque thickening = none or possible thickening but difficult to ascertain there is a slight elevation above normal skin level Scaling = none or residual surface dryness and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of the lesions Erythema = very bright red coloration; extremer red coloration; deep red coloration

3.2.2 Statistical Methodologies

The primary analysis population was the intent-to-treat (ITT) population, defined as all randomized subject. The applicant also conducted supportive analyses using the per-protocol (PP) population, defined by excluding subjects from the ITT population who:

- Receive no treatment with trial medication
- Provide no efficacy data following start of treatment
- Known to have taken the wrong trial medication throughout the treatment phase
- Do not fulfill the disease defining inclusion criteria

For Study 7, the protocol specified pooling centers that enrolled fewer than 18 subjects to form a pooled center of 18 or more subjects; however, the applicant pooled centers based on geographic location and the pooling resulted in 5 pooled centers with less than 18 subjects. For Study 1001, the protocol specified pooling centers that enrolled fewer than 16 subjects to form a pooled center of 16 or more subjects. The applicant pooled based on geographic location and the pooling resulted in all pooled centers with 16 or more subjects.

In both studies, the protocol-specified analysis method for the primary endpoint (i.e., treatment success at Week 4) was the Cochran-Mantel-Haenszel (CMH) test stratified by pooled center. The Breslow-Day test at $\alpha = 0.10$ level was used to investigate the center-to-center variability. If significant, the protocol specified conducting a sensitivity analysis where the pooled centers with the smallest and largest odds ratio are removed from the data.

For Study 7, the primary imputation method for handling missing data specified in the protocol was the last observation carried forward (LOCF) approach. The protocol did not specify any sensitivity analyses for the handling of missing data; therefore, this reviewer conducted

sensitivity analyses where missing data was imputed using the primary imputation method and sensitivity analyses (except for the approach based on vehicle treated subjects) that were pre-specified for Study 1001, see below.

For Study 1001, the primary imputation method specified in the protocol was the multiple imputation (MI) approach. Missing IGA values at Week 4 were imputed using ordinal logistic regression with treatment, IGA values at previous visits, and pooled centers in the model. The applicant conducted the following sensitivity analyses for handling of missing data:

- Impute missing data using "control-based pattern imputation", a multiple imputation approach where the imputation model used to impute the missing data is based only on the data from vehicle treated subjects
- Impute missing data using LOCF
- Impute missing data as non-responders
- Complete case analysis

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Study 7 enrolled and randomized a total of 302 subjects (100 to Enstilar®, 101 to BDP monad, and 101 to calcipotriene monad) from 28 centers in the United States. Study 1001 enrolled and randomized a total of 426 subjects (323 to Enstilar® and 103 to vehicle) from 27 centers in the United States. Table 5 presents the disposition of subjects for each study. While the discontinuation rates were generally similar across the treatment arms within each study, the discontinuation rates were slightly higher in Study 7 compared to Study 1001.

The demographics and baseline disease characteristics are displayed in Table 6. For Study 7, the demographics and baseline disease characteristics were generally balanced across the treatment arms. For Study 1001, subjects in the vehicle arm were on average slightly younger than subjects in the Enstilar® arm. In addition, there was a higher proportion of male subjects in the Enstilar® arm compared to the vehicle arm (i.e., 63% vs. 48%).

Table 5: Disposition of Subjects (ITT)

	Study 7			**Study 1001**	
	Enstilar® Foam (N=100)	**BDP in Vehicle (N=101)**	**Calcipotriene in Vehicle (N=101)**	**Enstilar® Foam (N=323)**	**Vehicle Foam (N=103)**
Discontinued	6 (6.0%)	7 (6.9%)	8 (7.9%)	10 (3.1%)	4 (3.9%)
Adverse Event	2	0	2	0	0
Lost to Follow-Up	2	5	5	7	1
Other	2	0	0	1	1
Voluntary	0	2	1	2	2

Source: Reviewer's Analysis

Table 6: Demographics and Baseline Disease Characteristics (ITT)

	Study 7			Study 1001	
	Enstilar® Foam (N=100)	**BDP in Vehicle (N=101)**	**Calcipotriene in Vehicle (N=101)**	**Enstilar® Foam (N=323)**	**Vehicle Foam (N=103)**
Age					
Mean (SD)	47.4 (14.8)	49.0 (14.4)	50.7 (14.7)	51.2 (13.9)	46.0 (13.2)
Median	49.0	50.0	51.0	52.0	46.0
Range	20 - 81	20 - 85	21 - 85	18 - 87	19 - 79
Gender					
Male	53 (53.0%)	56 (55.4%)	61 (60.4%)	204 (63.2%)	49 (47.6%)
Female	47 (47.0%)	45 (45.6%)	40 (39.6%)	119 (36.8%)	54 (52.4%)
Race					
White	93 (93.0%)	83 (82.2%)	92 (91.1%)	276 (85.4%)	90 (87.4%)
Black	6 (6.0%)	8 (7.9%)	4 (4.0%)	24 (7.4%)	6 (5.8%)
Asian	1 (1.0%)	5 (5.0%)	3 (3.0%)	10 (3.1%)	3 (2.9%)
Other	0	5 (5.0%)	2 (2.0%)	13 (4.0%)	4 (3.9%)
Ethnicity					
Hispanic or Latino	23 (23.0%)	20 (19.8%)	22 (21.8%)	85 (26.3%)	22 (21.4%)
Not Hispanic or Latino	77 (77.0%)	81 (80.2%)	79 (78.2%)	238 (73.7%)	81 (78.6%)
IGA (Trunk/Limbs)					
2 - Mild	11 (11.0%)	16 (15.8%)	14 (13.9%)	50 (15.5%)	15 (14.6%)
3 - Moderate	77 (77.0%)	75 (74.3%)	78 (77.2%)	244 (75.5%)	75 (72.8%)
4 - Severe	12 (12.0%)	10 (9.9%)	9 (8.9%)	29 (9.0%)	13 (12.6%)
Percent BSA (Trunk/Limbs)					
Mean (SD)	6.7 (4.9)	7.6 (6.3)	7.2 (5.6)	7.4 (6.4)	8.0 (7.0)
Median	5.0	5.0	5.0	5.0	5.0
Range	2 - 28	2 - 28	2 - 27	2 - 30	2 - 30
m-PASI (Trunk/Limbs)					
Mean (SD)	7.9 (4.5)	7.2 (3.9)	7.7 (4.4)	7.4 (4.8)	7.9 (6.6)
Median	6.7	6.3	6.4	6.0	6.1
Range	2 - 28	2.1 - 19.8	2.1 - 25.6	2 - 36.6	2 - 47.4

Source: Reviewer's Analysis
SD: Standard Deviation

3.2.4 Primary Efficacy Results

Table 7 presents results for the primary efficacy endpoint at Week 4 for both studies in the ITT population. In Study 7, Enstilar® foam was statistically superior to both the BDP monad ($p = 0.047$) and the calcipotriene monad ($p < 0.001$). In Study 1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$). The response rate for Enstilar® foam was lower in Study 7 compared to Study 1001 (i.e., 45% vs. 53%).

The results in the PP population are presented in Table 8. While the response rates in the PP population are similar to those in the ITT population, the comparison between Enstilar® foam and the BDP monad is no longer statistically significant ($p = 0.104$); however, this could be due to the decrease in sample size.

Table 7: Primary Efficacy Results at Week 4 (ITT, LOCF[1], MI[2])

	Enstilar® Foam	Betamethasone dipropionate in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Study 7	(N=100)	(N=101)	(N=101)	-
Treatment Success[3] Rate	45 (45.0%)	31 (30.7%)	15 (14.9%)	-
P-value[4]	-	0.047	<0.001	-
Study 1001	(N=323)	-	-	(N=103)
Treatment Success[3] Rate[5]	172.1 (53.3%)	-	-	4.9 (4.8%)
P-value[4]	-	-	-	<0.001

Source: Reviewer's Analysis
(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).
(2) Missing data for Study 1001 was imputed using multiple imputation (MI).
(3) Treatment success is defined as an IGA score of 0 or 1 with at least 2-grade improvement from baseline.
(4) P-value based on a CMH test stratified by pooled centers.
(5) Rates displayed are the averages over the 1000 imputed datasets.

Table 8: Primary Efficacy Results at Week 4 (PP)

	Enstilar® Foam	BDP in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Study 7	(N=79)	(N=86)	(N=81)	-
Treatment Success[1] Rate	37 (46.8%)	29 (33.7%)	13 (16.0%)	-
P-value[2]	-	0.104	<0.001	-
Study 1001	(N=302)	-	-	(N=96)
Treatment Success[1] Rate	162 (53.6%)	-	-	4 (4.2%)
P-value[2]	-	-	-	<0.001

Source: Reviewer's Analysis
(1) Treatment success is defined as an IGA score of 0 or 1 with at least 2-grade improvement from baseline.
(2) P-value based on a CMH test stratified by pooled centers.

3.2.5 Handling of Missing Data

Table 9 provides the number of subjects with missing data for the primary efficacy endpoint by week and treatment arm for each study. The proportion of subjects with missing data at Week 4 (i.e., the primary efficacy timepoint) was higher in Study 7 compared to Study 1001.

Table 9: Missing Data for the Primary Efficacy Endpoint by Week (ITT)

	Study 7			Study 1001	
	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Week 1	1 (1.0%)	6 (5.9%)	3 (3.0%)	7 (2.2%)	1 (1.0%)
Week 2	0 (0%)	4 (4.0%)	5 (5.0%)	8 (2.5%)	2 (2.0%)
Week 4	5 (5.0%)	7 (6.9%)	7 (6.9%)	10 (3.1%)	4 (3.9%)

Source: Reviewer's Analysis

Table 10 presents the results for the primary efficacy endpoint at Week 4 by the various imputation methods for Study 7. Although the response rates for each treatment arm were generally similar between the various imputation methods and the trend still favors the Enstilar® foam arm, the comparison between Enstilar® foam and the BDP monad was only statistically

significant at the 0.05 level when the missing data was imputed using LOCF. This could be due to the relatively small sample sizes in each treatment arm.

Table 10: Results for Primary Efficacy Endpoint at Week 4 with Different Approaches for Handling Missing Data in Study 7 (ITT)

	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)
LOCF (primary)	45 (45.0%)	31 (30.7%)	15 (14.9%)
P-value(1)	-	0.047	<0.001
MI-MCMC(2)	46.1 (46.1%)	33.5 (33.2%)	16.2 (16.1%)
P-value(1)	-	0.086	<0.001
Non-responder	44 (44.0%)	31 (30.7%)	14 (13.9%)
P-value(1)	-	0.064	<0.001
Observed	44/95 (46.3%)	31/94 (33.0%)	14/94 (14.9%)
P-value(1)	-	0.078	<0.001

Source: Reviewer's Analysis
(1) P-value based on a CMH test stratified by pooled centers.
(2) Rates displayed are the averages over the 1000 imputed datasets.

Table 11 presents the results for the primary efficacy endpoint at Week 4 by the various imputation methods for Study 1001. The results were similar across the various methods for handling missing data.

Table 11: Results for Primary Efficacy Endpoint at Week 4 with Different Approaches for Handling Missing Data in Study 1001 (ITT)

	Enstilar® Foam (N=323)	Vehicle Foam (N=103)	P-Value
MI-MCMC (primary)(2)	172.1 (53.3%)	4.9 (4.8%)	<0.001
MI-Vehicle(2)	168.1 (52.0%)	4.7 (4.5%)	<0.001
Non-responder	167 (51.7%)	4 (3.9%)	<0.001
LOCF	168 (52.0%)	5 (4.9%)	<0.001
Observed	167/313 (53.4%)	4/99 (4.0%)	<0.001

Source: Reviewer's Analysis
(1) P-value based on a CMH test stratified by pooled centers.
(2) Rates displayed are the averages over the 1000 imputed datasets.

3.3 Evaluation of Safety

3.3.1 Extent of Exposure

The extent of exposure to study product is presented in Table 12. The planned duration of exposure in both studies was 4 week. The duration of exposure was similar between the treatment arms within each study and between each study. The amount of study product within each study was generally similar between the treatment arms; however, the amount of product used in Study 1001 was on average less than the amount of product used in Study 7.

Table 12: Extent of Exposure (Safety Population)

	Study 7			Study 1001	
	Enstilar® Foam (N=100)	**BDP in Vehicle (N=99)**	**Calcipotriene in Vehicle (N=99)**	**Enstilar® Foam (N=323)**	**Vehicle Foam (N=103)**
Duration of Exposure (weeks)					
Mean (SD)	4.1 (0.7)	4.0 (0.6)	4.1 (0.8)	4.0 (0.6)	4.1 (0.6)
Range	1.0 – 6.0	0.6 – 5.6	0.7 – 6.9	0.1 – 6.0	0.1 – 6.3
Weekly Amount of Product Used (g/week)					
N	93	90	88	293	98
Mean (SD)	32.9 (21.6)	35.8 (22.3)	35.4 (21.7)	29.8 (21.2)	32.1 (23.6)
Median	29.2	30.5	32.3	24.1	23.1
Range	4.0 – 83.6	5.4 – 89.0	5.0 – 84.0	2.1 – 89.7	2.5 – 87.7
Total Amount of Product Used (g)					
N	93	90	88	293	98
Mean (SD)	134.2 (89.9)	145.4 (92.1)	145.8 (91.4)	120.8 (85.7)	128.9 (92.9)
Median	118.6	122.6	129.0	100.2	98.0
Range	19.0 – 346.2	4.9 – 355.8	6.0 – 339.9	8.2 – 346.1	9.4 – 350.7

Source: pg. 122, 123 and 197 of Study Report for Study 7, and pg. 88, 89 and 90 of Study Report for Study 1001.
SD: Standard Deviation

3.3.2 Adverse Events

Table 13 presents an overview of the adverse events reported in Studies 7 and 1001. The adverse reactions reported in both studies by system organ class and preferred term are presented in Table 14.

Table 13: Overview of Adverse Events Reported (Safety Population)

	Study 7			Study 1001	
Subjects With:	**Enstilar® Foam (N=100)**	**BDP in Vehicle (N=99)**	**Calcipotriene in Vehicle (N=99)**	**Enstilar® Foam (N=323)**	**Vehicle Foam (N=103)**
Any AEs	11 (11.0%)	13 (13.1%)	10 (10.1%)	51 (15.8%)	12 (11.7%)
Adverse Drug Reactions	4 (4.0%)	7 (7.1%)	6 (6.1%)	10 (3.1%)	2 (1.9%)
Any Severe AEs	1 (1.0%)	0	0	5 (1.5%)	0
Any Serious AEs	1 (1.0%)	0	0	2 (0.6%)	0
Any AEs Leading to Withdrawal	2 (2.0%)	0	2 (2.0%)	0	0

Source: pg. 125 of Study Report for Study 7 and pg. 88 of Study Report for Study 1001.

Table 14: Adverse Reactions Reported in Studies 7 and 1001 (Safety Population)

System Organ Class / Preferred Term	Study 7			Study 1001	
	Enstilar® Foam (N=100)	BDP in Vehicle (N=99)	Calcipotriene in Vehicle (N=99)	Enstilar® Foam (N=323)	Vehicle (N=103)
Gastrointestinal disorders					
Buccal mucosal roughening	1 (1%)	0	0	0	0
Diarrhoea	0	1 (1%)	0	0	0
General disorders and administration site conditions					
Application site discoloration	0	0	0	1 (0.3%)	0
Application site dryness	0	0	0	0	1 (1%)
Application site erosion	0	0	1 (1%)	0	1 (1%)
Application site erythema	0	0	1 (1%)	0	1 (1%)
Application site irritation	0	0	0	1 (0.3%)	0
Application site oedema	0	0	1 (1%)	0	1 (1%)
Application site pain	1 (1%)	1 (1%)	1 (1%)	2 (0.6%)	1 (1%)
Application site pruritus	0	0	0	1 (0.3%)	0
Application site reaction	0	0	0	1 (0.3%)	0
Medication residue	0	3 (3.0%)	2 (2.0%)	0	0
Immune system disorders					
Hypersensitivity	1 (1.0%)	0	1 (1%)	0	0
Infections and infestations					
Folliculitis	0	0	0	1 (0.3%)	0
Staphylococcal infection	0	1 (1%)	0	0	0
Tinea infection	0	0	1 (1%)	0	0
Investigations					
Urine calcium/creatinine ratio increase	0	0	1 (1%)	1 (0.3%)	0
Skin and subcutaneous tissue disorders					
Alopecia	1 (1%)	0	0	0	0
Alopecia effluvium	0	1 (1%)	0	0	0
Dermatitis contact	0	0	1 (1%)	0	0
Psoriasis	0	0	0	1 (0.3%)	0
Pruritus	0	1 (1%)	0	0	0
Skin irritation	0	0	0	1 (0.3%)	0

Source: pg. 130 of Study Report for Study 7 and pg. 129 of Study Report for Study 1001.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, Race, and Baseline Disease Severity

Tables 15 and 16 present the results for the primary efficacy endpoint at Week 4 by age (< 65 vs. ≥ 65), gender, race (white vs. non-white), and baseline disease severity (IGA) subgroups for Studies 7 and 1001, respectively. In both studies, the response rate for the Enstilar® foam was generally consistent across the age, gender and race subgroups. In addition, the response rate for the Enstilar® foam arm was consistently higher than the other treatment arms across these subgroups in both studies. For Study 7, the response rate for the Enstilar® foam arm was lower

than the BDP arm in subjects with a baseline IGA score of 4 (severe); however, a small proportion of subjects (10%) had a baseline IGA score of 4.

Table 15: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Study 7 (ITT, LOCF[(1)])

Subgroup (N_E, N_{BDP}, N_C)	Enstilar® Foam (N=100)	BDP in Vehicle (N=101)	Calcipotriene in Vehicle (N=101)
Age			
< 65 (88, 88, 81)	44.3%	28.4%	13.6%
≥ 65 (12, 13, 20)	50.0%	46.2%	20.0%
Gender			
Male (53, 56, 61)	43.4%	28.6%	18.0%
Female (47, 45, 40)	46.8%	33.3%	10.0%
Race			
White (93, 83, 92)	45.2%	30.1%	14.1%
Non-White (7, 18, 9)	42.9%	33.3%	22.2%
IGA			
2 – Mild (11, 16, 14)	45.5%	18.8%	0%
3 – Moderate (77, 75, 78)	49.4%	32.0%	19.2%
4 – Severe (12, 10, 9)	16.7%	40.0%	0%

Source: Reviewer's Analysis
(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).

Table 16: Primary Efficacy Results at Week 4 by Age, Gender, Race and Baseline Disease Severity for Study 1001 (ITT, MI[(1)])

Subgroup (N_E, N_V)	Enstilar® Foam (N=323)	Vehicle Foam (N=103)
Age		
< 65 (260, 93)	52.5%	5.3%
≥ 65 (63, 10)	56.5%	0%
Gender		
Male (204, 49)	56.8%	5.9%
Female (119, 54)	47.3%	3.7%
Race		
White (276, 90)	53.8%	4.3%
Non-White (47, 13)	50.0%	7.7%
IGA		
2 – Mild (50, 15)	30.2%	0.2%
3 – Moderate (244, 75)	59.8%	5.2%
4 – Severe (29, 13)	37.9%	7.7%

Source: Reviewer's Analysis
(1) Missing data for Study 1001 was imputed using multiple imputation (MI).
(2) Rates displayed are the averages over the 1000 imputed datasets.

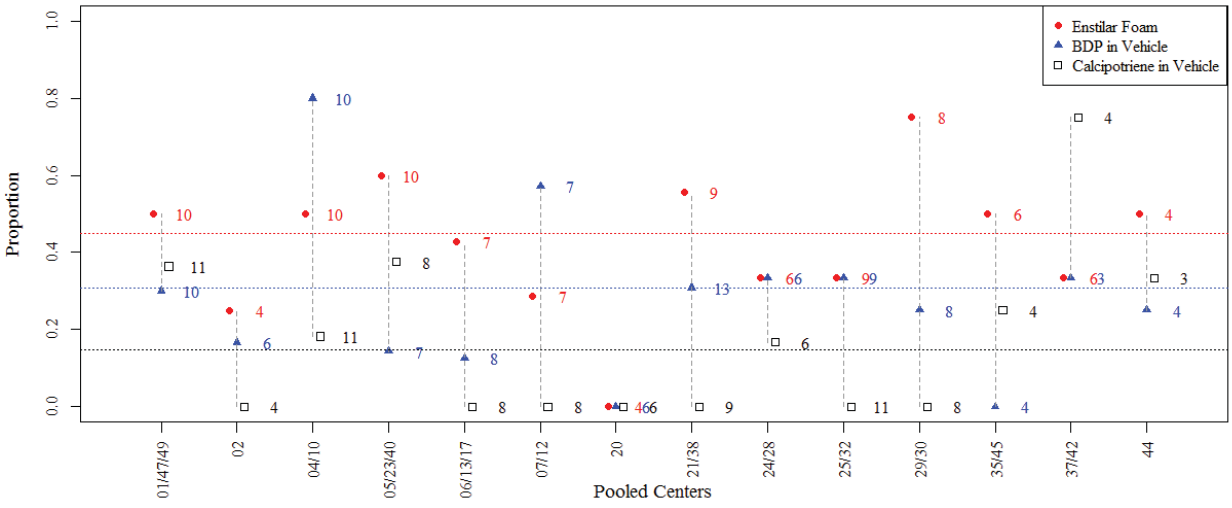
4.2 Center

Studies 7 and 1001 enrolled subjects from 28 and 27 centers (all in United States), respectively. For Study 7, the protocol specified pooling centers that enrolled fewer than 18 subjects to form a pooled center of 18 or more subjects. The applicant pooled centers based on geographic location and the pooling resulted in 14 pooled centers; however, 5 pooled centers have less than 18 subjects. For Study 1001, the protocol specified pooling centers that enrolled fewer than 16 subjects to form a pooled center of 16 or more subjects. The applicant pooled based on geographic location and the pooling resulted in 19 pooled centers (all with 16 or more subjects).

Figures 1 and 2 present the results for the primary efficacy endpoint at Week 4 by pooled centers for Studies 7 and 1001, respectively. Per the protocol, the applicant conducted the Breslow-Day test for homogeneity of the odds ratio across pooled centers at $\alpha = 0.10$ level for primary endpoint at Week 4. For Study 7, the p-value for the Breslow-Day test was 0.27 for the comparison of Enstilar® foam to the BDP monad and 0.13 for the comparison of Enstilar® foam to the calcipotriene monad. For Study 1001, the p-value for the Breslow-Day test was 0.14.

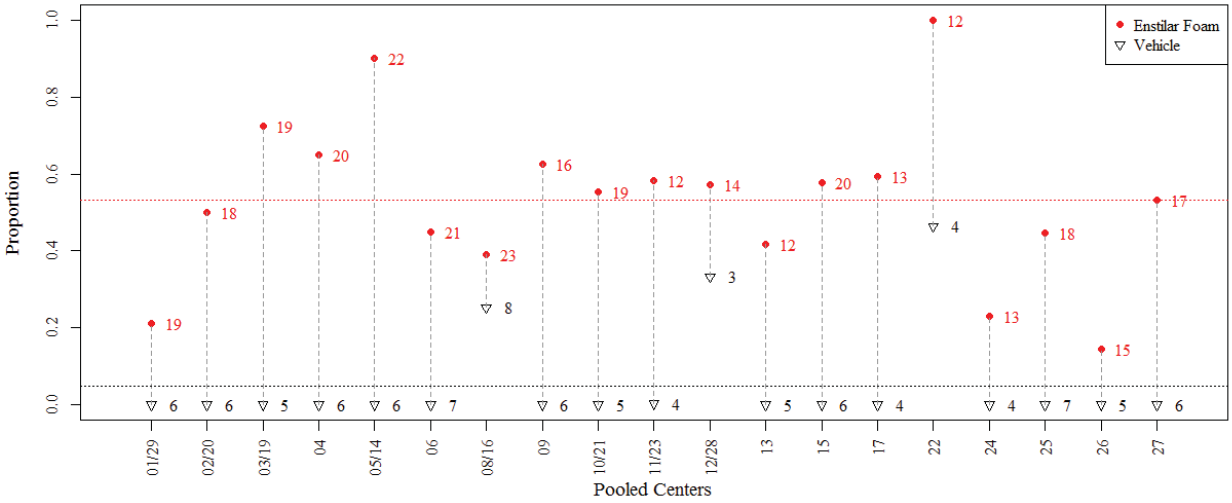
For Study 7, the response rates were variable across pooled centers; however, no pooled center was overly influential on the overall results. For Study 1001, the response rates for Enstilar® foam were consistently higher than vehicle and no pooled center overly influential on the overall results. As the pooling process could mask center effects, this reviewer conducted a sensitivity analysis where each center (prior to pooling) was removed. For Study 7, the overall response rates were similar no matter which center was removed. For Study 1001, the removal of any one center did not affect the overall conclusions (p-values ≤ 0.001).

Figure 1: Primary Efficacy Results at Week 4 by Pooled Center for Study 7 (ITT, LOCF[(1)])



Source: Reviewer's Analysis
(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).

Figure 2: Primary Efficacy Results at Week 4 by Pooled Center for Study 1001 (ITT, MI[(1)])



Source: Reviewer's Analysis
(1) Missing data for Study 1001 was imputed using multiple imputation (MI).
(2) Rates displayed are the averages over the 1000 imputed datasets.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The applicant submitted data from one Phase 3 trial (Study 1001) and two Phase 2 trials (Study 7 and Study 35) to establish the safety and efficacy of Enstilar® foam. The applicant designated Studies 7 and 1001 as pivotal/confirmatory trials and Study 35 as a supportive trial. Study 7 compared Enstilar® foam to the two monads (no vehicle arm) and Study 1001 compared Enstilar® foam to vehicle foam (no monad arms). Study 35 compared Enstilar® foam to Taclonex® ointment, vehicle foam and vehicle ointment. The inclusion and exclusion criteria were similar among the studies. Subjects must have had an IGA score of at least mild, involving 2-30% BSA at baseline. It should be noted that the requirement of 2-30% BSA in Study 1001 and Study 35 included only trunk and limbs whereas in Study 7 also included the scalp.

The protocol-specified primary efficacy endpoint was the proportion of subjects with 'treatment success' at Week 4, where treatment success is defined as an IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade improvement from baseline. Table 17 presents the primary efficacy results for Studies 7 and 1001. In Study 7, Enstilar® foam was statistically superior to both the BDP foam monad ($p = 0.047$) and the calcipotriene foam monad ($p < 0.001$). In Study 1001, Enstilar® foam was statistically superior to vehicle foam ($p < 0.001$). The results for Study 35 are presented in Table A.1 in the Appendix and are supportive of those observed in Studies 7 and 1001.

There were no major statistical issues affecting overall conclusions. For the handling of missing data, the response rates were similar between the primary imputation methods and the sensitivity analyses. Treatment effects were generally consistent across subgroups.

Table 17: Primary Efficacy Results at Week 4 (ITT, LOCF[(1)], MI[(2)])

	Enstilar® Foam	Betamethasone dipropionate in Vehicle Foam	Calcipotriene in Vehicle Foam	Vehicle Foam
Study 7	(N=100)	(N=101)	(N=101)	-
Treatment Success[(3)] Rate	45 (45.0%)	31 (30.7%)	15 (14.9%)	-
P-value[(4)]	-	0.047	<0.001	-
Study 1001	(N=323)	-	-	(N=103)
Treatment Success[(3)] Rate[(5)]	172.1 (53.3%)	-	-	4.9 (4.8%)
P-value[(4)]	-	-	-	<0.001

Source: Reviewer's Analysis
(1) Missing data for Study 7 was imputed using last observation carried forward (LOCF).
(2) Missing data for Study 1001 was imputed using multiple imputation (MI).
(3) Treatment success is defined as an IGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(4) P-value based on a CMH test stratified by pooled centers.
(5) Rates displayed are the averages over the 1000 imputed datasets.

For Study 1001, the applicant reported that a center (US15; Dr. Jane Lee) did not perform assessments as specified in the protocol. This review conducted a sensitivity analysis where all subjects from this center were removed. The results were similar with and without center #15, and the center did not affect the overall conclusion.

5.2 Conclusions and Recommendations

Efficacy findings from two trials (Studies 7 and 1001) established the efficacy of Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% for the topical treatment of plaque psoriasis.

APPENDIX

Study 35 was a randomized, multicenter, investigator-blind, parallel-group, active and vehicle-controlled, 4-week, Phase 2 trial in subjects with mild to severe plaque psoriasis. Eligible subjects were randomized to one of the following treatment arms in a 3:3:1:1 ratio: Enstilar® foam, Taclonex® ointment, vehicle foam, and vehicle ointment.

A total of 376 subjects were enrolled and randomized (141 to Enstilar® foam, 135 to Taclonex® ointment, 49 to vehicle foam, and 51 to vehicle ointment) from 35 centers in the United States. The randomization was stratified by baseline disease severity (IGA=2 or IGA≥3). Subjects were evaluated at baseline (Week 0) and Weeks 1, 2, and 4.

The results for the primary efficacy endpoint at Week 4 are presented in Table A.1. Enstilar® foam was statistically superior (p = 0.025) to Taclonex® ointment. It should be noted that the comparison between Enstilar® foam and vehicle foam was not pre-specified in the protocol and therefore is a post-hoc analysis.

Table A.1: Primary Efficacy Results at Week 4 for Study 35 (ITT, LOCF[(1)])

	Enstilar® Foam (N=141)	**Taclonex® Ointment (N=135)**	**Vehicle Foam (N=49)**	**Vehicle Ointment (N=51)**
Treatment Success[(2)] Rate	77 (54.6%)	58 (43.0%)	3 (6.1%)	4 (7.8%)
P-value[(3)]	-	0.025	<0.001	-

Source: Reviewer's Analysis

(1) Missing data was imputed using last observation carried forward (LOCF).
(2) Treatment success is defined as an IGA score of 0 or 1 with at least a 2-grade improvement from baseline.
(3) P-value based on a CMH test stratified by pooled centers.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Matthew Guerra, Ph.D.
Date: September 2, 2015

Statistical Team Leader: Mohamed Alosh, Ph.D.
Date: September 2, 2015

cc:
DDDP/Marcus
DDDP/Lindstrom
DDDP/Diglisic
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DDDP/Gould
DDDP/Williams
OBIO/Patrician
DBIII/Wilson
DBIII/Alosh
DBIII/Guerra

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/s/

MATTHEW W GUERRA
09/02/2015

MOHAMED A ALOSH
09/02/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 207589 **Applicant:** LEO Pharma A/S **Stamp Date:** 12/18/2014

Drug Name: Enstilar® (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064% **NDA/BLA Type:** 505(b)(1)

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			
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

Matthew Guerra, Ph.D.	February 6, 2015
Reviewing Statistician	Date
Mohamed Alosh, Ph.D.	February 6, 2015
Supervisor/Team Leader	Date

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

/s/

MATTHEW W GUERRA
02/06/2015

MOHAMED A ALOSH
02/06/2015