Global Assessment of Improvement (As Per Subject)—for the whole scalp

Score	Category
5	Clear
4	Almost clear
3	Marked improvement
2	Moderate improvement
1	Minimal improvement
0	No change
-1	Worse

Source: Sponsor's NDA submission vol. 1.33 p. 4434

Reviewer's Comment: *The endpoint Global Assessment of Improvement per Subject used a dynamic scale that lacks definition. Dynamic scales are subject to recall bias, and differing values and category interpretations among subjects complicate self-assessments. The Sponsor has not submitted evidence regarding the validation of this instrument. This endpoint will not be reviewed.*

Results

A total of 148 subjects from 12 study centers were enrolled and randomized into the study to receive either Clobetasol Propionate Shampoo, 0.05% or Clobetasol Propionate Shampoo Vehicle. Enrollment exceeded protocol specifications as 16 subjects were enrolled and randomized prior to notification that target enrollment had been achieved. Table 8 shows the subject disposition.

Table 8: Disposition of Study Subjects, Study RD.06.SRE.18075

Disposition	**Clobetasol Propionate Shampoo, 0.05% N (%)**	**Clobetasol** Propionate **Shampoo Vehicle N (%)**	**Total N (%)**
Enrolled	99 (100)	49 (100)	148 (100)
Randomized	99 (100)	49 (100)	148 (100)
ITT population	99 (100)	49 (100)	148 (100)
PP population	91 (91.9)	43 (87.8)	134 (90.5)
Safety population	98 (99.0)	48 (98.0)	146 (98.6)
Completed study	91 (91.9)	45 (91.8)	136 (91.6)
Discontinued	8 (8.1)	4 (8.2)	12 (8.1)
Lack of efficacy	0 (0)	1 (2.0)	1 (0.7)
Adverse event	2 (2.0)	1 (2.0)	3 (2.0)
Subject request	3 (3.0)	2 (4.1)	5 (3.4)
Protocol violation	1 (1.0)	0 (0)	1 (0.7)
Lost to follow-up	2 (2.0)	0 (0)	2 (1.4)

Source: Sponsor's NDA submission vol 1.33, p. 4446.

Among the 148 randomized subjects, 14 were found to have violated the protocol after receiving study medication and were not included in the PP (per protocol) population. Reasons included missing 2 or more visits (6 active and 1 vehicle subject/s), receiving prohibited concomitant medication (2 active and 3 vehicle subjects), no post-baseline data (2 vehicle subjects).

Reviewer's Comment: *The Division and Sponsor agreed that the primary endpoint would be assessed for the intent-to-treat (ITT) population. The review will focus on the ITT population.*

Patient demographics are outlined in Table 9.

Table 9: Demographic Characteristics of Study Subjects - ITT Population, Study 18075

Demographic Parameter	**Clobetasol** Propionate **Shampoo 0.05% N=99 (67%)**	**Clobebetasol Propionate Shampoo Vehicle N=49(33%)**	**Total N=148(100%)**	**p-value**
Gender				
Male	46 (46.5)	20 (40.8)	66 (44.6)	0.482
Female	53 (53.5)	29 (59.2)	82 (55.4)	
Race				
Caucasian	85 (85.9)	45 (91.8)	130 (87.8)	
Black	3 (3.0)	1 (2.0)	4 (2.7)	
Asian	2 (2.0)	0 (0)	2 (1.4)	0.736
Hispanic	8 (8.1)	3 (6.1)	11 (7.4)	
Other	1 (1.0)	0 (0)	1 (0.7)	
Age (mean)	47.1	46.4	46.9	0.801
Age ranges (yrs)				
12 to 17 years	3 (3.0)	3 (6.1)	6 (4.1)	
18 to 64 years	80 (80.8)	37 (75.5)	117 (79.1)	0.631
≥65 years	16 (16.2)	9 (18.4)	25 (16.9)	

Source: Sponsor's NDA submission, vol. 1.33 p.4449.

Reviewer's Comment: *Age, race and gender appear to be comparably distributed between the active and vehicle groups.*

Baseline disease severity is outlined in Table 10

Table 10: Global Severity at Baseline

Global Severity Score *descriptor (numeric score)*	**Clobetasol** Propionate **Shampoo 0.05% N=99** *n(%)*	**Clobebetasol Propionate Shampoo Vehicle N=49** *n(%)*	**p-value**
Moderate (3)	76 (76.8)	35 (71.4)	
Severe (4)	20 (20.2)	13 (26.5)	0.455
Very Severe (5)	3 (3.0)	1 (2.0)	

Source: Sponsor's NDA submission, vol 1.33 p.4455.

Reviewer's Comment: *Baseline disease severity as measured by the Global Severity Scale was similar for both study arms. The majority of patients (>70% in both arms) had moderate scalp psoriasis.*

Efficacy Endpoint Outcomes

The results of the primary efficacy variable, success in Global Severity at the week 4 endpoint, are presented in Table 11.

Table 11: Number of Patients with Success in Global Severity at Week 4, Study 18075

Population	Clobetasol Propionate Shampoo, 0.05% n/N(%)	Clobetasol Propionate Shampoo Vehicle n/N(%)	p-value
ITT	27/89 (30.3)	5/45 (11.1)	0.013
ITT (LOCF)	**28/99 (28.3)**	**5/29 (10.2)**	**0.012**
PP	27/88 (30.7)	4/42 (9.5)	0.008
PP (LOCF)	28/91 (30.8)	4/43 (9.3)	0.007

Source: Sponsor'NDA submission, Vol 1.33, pp. 4518-9.
N=total number of evaluable subjects at week 4
n=number of subjects with success
ITT=intent to treat
PP=per protocol
LOCF=last observation carried forward

The results of the relevant secondary efficacy variables are delineated in table 12.

Table 12: Secondary Efficacy Variables at Week 4 Endpoint ITT (LOCF) Population, Study 18075

Variable	Clobetasol Propionate Shampoo, 0.05% N=99	Clobetasol Propionate Shampoo Vehicle N=49	p-value
Erythema: none or mild *n(%)*	62 (62.6)	20 (40.8)	0.0070
Scaling: none *n(%)*	15 (15.2)	2 (4.1)	0.0317
Plaque thickening: none *n(%)*	34 (34.3)	5 (10.2)	0.0005
Pruritus: none *n(%)*	41 (41.4)	8 (16.3)	0.0021

Source: Sponsor's NDA submission vol. 1.33 p. 4458, and FDA Biostatistician's analysis.

Reviewer's Comment: *In the pivotal trial Study 18075, Clobetasol Shampoo was superior to its vehicle for the primary efficacy endpoint success in global severity for the ITT (LOCF) population (p-value 0.012); this also held true for the PP (LOCF) population (p-value 0.007). The secondary endpoints were supportive in that proportion of subjects who achieved success for erythema, scaling and plaque thickening were significantly greater in the Clobetasol Shampoo arm than the vehicle shampoo arm (p-values of 0.005, 0.012, 0.006 respectively). Additionally, the proportion of sujbects with resolution of pruritus was significantly greater in the active versus the vehicle arms (p-value 0.001).*

Pivotal Study #2: Protocol Number: RD.06.SRE.**18076**

Title: "A Randomized, Double-Blind, Parallel Group Evaluation of Clobetasol Propionate Shampoo, 0.05% Versus Its Vehicle – An Efficacy and Safety Study in Subjects with Scalp Psoriasis"

Investigators

Analysis Center	Investigator Number/Name/Location	Patients Enrolled Active/Vehicle/Total
01		12/6/18
02	0439/Michael Jarratt, MD/Austin, TX	10/5/15
03		10/5/15
04		9/5/14
05		9/4/13
06		7/3/10
07		6/3/9
08		6/3/9
09		6/3/9
10		5/3/8
11		4/3/7
12		6/2/8
12		5/2/7

Reviewer's Comment: *Enrollment in some centers was low. The Sponsor combined centers 0438 and 2151 for analysis.*

Objective/Rationale

The primary objective of the study was to evaluate the efficacy and safety of Clobetasol Propionate Shampoo, 0.05%, vs. its corresponding vehicle, Clobetasol Propionate Shampoo Vehicle, in subjects aged 12 years and older with moderate to severe scalp psoriasis.

Overall Study Design

This study was conducted as a multi-center, randomized, vehicle-controlled, double-blinded, parallel-group comparison involving subjects aged 12 years and older with moderate to severe scalp psoriasis. Qualified subjects, who met specific enrollment criteria, were randomized in a 2:1 ratio to receive Clobetasol Propionate Shampoo, 0.005%, or Clobetasol Propionate Shampoo Vehicle, respectively. Subjects were dispensed two 4-oz bottles (approximately 120 gms) of study drug every two weeks; the amount of study drug applied per week by each subject was determined by weighing the bottles used during the treatment period. Subjects were to apply the study drug once daily to the affected areas of the scalp (then wait 15 minutes before lathering and rinsing) for a period of 4 weeks (or shorter if the condition cleared), with a 2-week

treatment-free follow-up period to assess psoriasis recurrence after treatment discontinuation. Subjects were evaluated at baseline and weeks 2, 4, and 6.

Reviewer's Comment: *Subjects who cleared before the week 4 endpoint were allowed to terminate treatment and enter the treatment-free follow-up period at the time of clearing, rather than continuing treatment to the week 4 endpoint, to avoid unnecessary exposure to a super-high potent topical steroid.*

Protocol

Inclusion Criteria

- Male or female subjects, 12 years of age or older.
- Female subjects of childbearing potential having a negative urine pregnancy test (UPT) at the beginning of the study. Pre-menses females and those who had undergone a hysterectomy, bilateral ovariectomy, or tubal ligation or had been post-menopausal for at least 2 years were not considered to be of childbearing potential.
- Subjects with moderate to severe scalp psoriasis (defined as global severity score of at least three: moderate plaque elevation, coarser scale with most lesions at least partially covered, moderate erythema with definite red coloration)
- Subjects who provided written informed consent and, if applicable, whose parent/guardian provided written informed consent.
- Subjects willing and capable of cooperating to the extent and degree required by the protocol.

Exclusion Criteria

- Subjects with medical conditions that would have put the subject at increased risk from study participation, confounded study assessments, or interfered with subject participation.
- Female subjects of childbearing potential not practicing an acceptable form of contraception (abstinence; implanted, injectable, or oral contraceptive; intrauterine contraceptive device, vasectomized partner).
- Subjects whose scalp psoriasis necessitates systemic or other concomitant topical therapies during the study (concomitant treatment of *body* psoriasis with topical emollients, coal tars, vitamin D derivatives, tazarotene, and salicylic acid was allowed).
- Allergy to one of the components of the test products
- Subjects who participated in a biomedical research trial in the month preceding enrollment.
- Subjects who were pregnant, nursing or planning a pregnancy.
- Subjects who used the following topical treatments on the scalp within the given washout periods
  - Topical corticosteroids 2 weeks
  - Topical anti-psoriatics (vit D derivatives, tazarotene, salicylic acid, coal tars) 2 weeks
- Subjects who used topical corticosteroids on the body within the two week washout period
- Subjects who used the following systemic treatments within the given washout periods
  - Systemic corticosteroids 4 weeks
  - Psoralen plus ultraviolet light (PUVA) therapy 6 weeks

- Systemic immunosuppressive drugs (such as azathioprine, methotrexate, cyclosporine, tacrolimus, mycophenolate) 8 weeks
- Systemic retinoids (such as isotretinoin, acitretin) 16 weeks
- Other treatment that could have aggravated psoriasis*:
  - β-blockers 2 weeks
  - Lithium preparations 2 weeks
  - Antimalarials 2 weeks
  - Nonsteroidal anti-inflammatory drugs 2 weeks
- Subjects who were known to be immunocompromised
- Subjects with a history of adverse response to topical or systemic steroid therapy
- Subjects with prolonged exposure to ultraviolet light during the 2-week period before study entry

*If the drug had been used for more than 6 months without worsening of the psoriasis, then the subject could have been included in the study.

Withdrawal Criteria

Reasons for withdrawal may have included but were not limited to the following:
- Psoriasis flare that needed an interfering therapy
- Pregnancy
- Investigator's request for safety reasons
- Subject's request
- Major protocol violation that would have confounded interpretation of results
- Loss to follow-up

Procedures and Observations

Each subject was to receive both verbal and written instructions as to the proper dosing and study medication application techniques at the time the study drug was dispensed during the baseline visit. The study agent was to be applied to affected areas of the scalp by moving the hair to expose the affected scalp, applying the study drug directly from the bottle onto the scalp, spreading the study drug to cover the entire lesion with a thin film and then repeating for each additional scalp lesion. The study drug was to be left in place for 15 minutes, then water added to lather and rinse thoroughly. The study agent was to be applied daily for a period of four weeks (or shorter if the condition cleared). At the conclusion of the treatment period (end of week four or time of clearing), a 2-week, treatment-free period commenced.

Table 13 documents the assessments that were to be made throughout the trial.

Table 13: Efficacy and Safety Evaluations

Parameter	Baseline	Week 2	Week 4	Week 6
Efficacy Variables				
Global Severity	X	X	X	X
Erythema	X	X	X	X

Scaling	X	X	X	X
Plaque Thickening	X	X	X	X
Pruritus	X	X	X	X
Scalp surface area of involvement	X	X	X	X
Global Assessment of Improvement-Investigator		X	X	
Global Assessment of Improvement-Subject		X	X	
Safety Variables				
Adverse Events	X	X	X	X
Source: Sponsor's NDA submission: Volume 1.39, page 6701				

Reviewer's Comment: *The Division agreed to Global Severity, dichotomized to success or failure, as the primary efficacy endpoint at the pre-IND/EOP-2 meeting. The Division has historically recognized the individual parameters of erythema, scaling and plaque thickening as relevant secondary endpoints for psoriasis. No agreement on secondary endpoints is mentioned in the preIND/EOP2 minutes or SPA, other than the need for statistical correction for multiple endpoints.*

Efficacy Endpoints

The primary efficacy variable was success rate versus failure rate, assessed for the ITT population. Success rate was defined as the proportion of subjects with a global severity score of clear or minimal. The Global Severity Scale is a static six-point integer scale (0 to 5) with morphologic descriptors, shown below in Table 14. The primary efficacy endpoint was week 4.

Table 14: Global Severity Scale

Score	Category	Category Description
0	Clear	Plaque thickening = none (no elevation or thickening over normal skin) Scaling = none (no evidence of scaling) Erythema = ± (hyperpigmentation or residual red coloration)
1	Minimal	Plaque thickening = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin level) Scaling = ± (residual surface dryness and scaling) Erythema = up to mild (up to light red or pink coloration)
2	Mild	Plaque thickening = slight (slight but definite elevation) Scaling = fine (fine scales partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque thickening = moderate (moderate elevation with rounded or sloped edges) Scaling = coarser (most lesions at least partially covered) Erythema = moderate (definite red coloration)
4	Severe	Plaque thickening = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (non-tenacious scale predominates, covering most or all of the lesions) Erythema = very severe (very bright red coloration)
5	Very Severe	Plaque thickening = very marked (very marked elevation typically with hard or sharp edges)

		Scaling = very coarse (thick tenacious scale covers most or all of the lesions) Erythema = very severe (extreme red coloration; deep red coloration)

Source: Sponsor's NDA submission vol 1.39 p.6920

Reviewer's Comment: *The Global Severity Scale above is an acceptable static integer scale with morphologic descriptors of approximately equal decrement delineating progressively worse disease. The Division's definition of success, clear or almost clear, corresponds with Grades 0 or 1, Clear or Minimal, on the Global Severity Scale. A baseline Global Severity score of 3, or Moderate, was necessary for enrollment. Hence a subject needed to improve by at least two units to achieve success (grade 0 or 1).*

The secondary efficacy variables include global severity (full scale, not dichotomized); total severity score (TSS), which is the sum of erythema, plaque thickening, and scaling scores; individual scores for erythema, plaque thickening, scaling, and pruritus; percent scalp surface area of involvement; global assessment of improvement by the investigator; and global assessment of improvement by the subject.

Total Severity Score (TSS): the sum of the individual scores for erythema, scaling, and plaque thickening. Each individual parameter was scored on a 4-point scale from 0 to 3 on the whole scalp.

Reviewer's Comment: *TSS is a computed score that is not clinically relevant. It is not used by clinicians to assess or follow patients with psoriasis. It is doubtful that a particular score or magnitude of change would be meaningful to practicing physicians or their patients. TSS will not be reviewed.*

Erythema (abnormal redness of the skin)

0	None	No erythema
1	Mild	Slight pinkness present
2	Moderate	Definite redness; easily recognized
3	Severe	Intense redness

Source: Sponsor's NDA submission vol 1.39 p.6921

Reviewer's Comment: *The Division has recognized erythema as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) or 1 (mild) on the above scale corresponds with clear or almost clear for erythema.*

Scaling (scales attached to the scalp)

0	None	No scale visible on the scalp
1	Mild	Some scales, which may often be fine, on the scalp
2	Moderate	Numerous flakes of scaling present on the scalp
3	Severe	Presence of very numerous flakes of scaling, usually large, on the scalp

Source: Sponsor's NDA submission vol. 1.39 p.6921

Reviewer's Comment: *The Division has recognized scaling as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) on the above scale corresponds with clear or almost clear for scaling.*

Plaque Thickening (a thickening or elevation of a circumscribed lesion or plaque)

0	None	No plaque thickening
1	Mild	Slight thickening
2	Moderate	Definite but not solid thickening
3	Severe	Marked, solid thickening

Source: Sponsor's NDA submission vol. 1.39 p.6921

Reviewer's Comment: *The Division has recognized plaque thickening as a meaningful secondary endpoint in psoriasis trials. A score of 0 (none) on the above scale corresponds with clear or almost clear for plaque thickening.*

Pruritus (an itching sensation)

0	None	No itching
1	Mild	Slight itching, not really bothersome
2	Moderate	Definite itching, somewhat bothersome, without loss of sleep
3	Severe	Intense itching that has caused pronounced discomfort; night rest interrupted. Excoriation of the skin from scratching may be present.

Source: Sponsor's NDA submission vol. 1.39 p.6922

Reviewer's Comment: *The Division has not historically recognized pruritus as a secondary endpoint in psoriasis trials. However, pruritus is often a symptom of scalp psoriasis.*

Scalp surface area: The method used to estimate the percent involved area was not described in the protocol.

Reviewer's Comment: *In comments provided to the Sponsor regarding IND 60,934 SN004, the medical reviewer informed the Sponsor that it was"... unclear from the protocol how surface area of involvement can be accurately estimated on the scalp."*[4] *No further elaboration was provided, and this reviewer is similarly uncertain about the accuracy of the estimations obtained. The endpoint Scalp Surface Area will not be reviewed.*

Global Assessment of Improvement (As Per Investigator)

Score	Category	Category Description
5	Clear	All signs and symptoms of disease have resolved (100% improvement from Baseline)
4	Almost clear	Nearly all signs and symptoms of disease have cleared (about 90% improvement from Baseline); only minimal residual signs and symptoms remain
3	Marked improvement	Majority of the signs and symptoms have resolved (about 75% improvement from Baseline)
2	Moderate	Significant improvement, but many signs and symptoms remain (about 50%

[4] Sponsor's NDA submission, vol. 1.1, p. lxxxix.

	improvement	improvement from Baseline)
1	Minimal improvement	Slight overall improvement, but not clinically significant (about 25% improvement from Baseline)
0	No change	Overall severity similar to baseline
-1	Worse	Worse than Baseline

Source: Sponsor's NDA submission vol. 1.39 p.6922

Reviewer's Comment: *The endpoint Global Assessment of Improvement per Investigator used a dynamic scale. Dynamic scales are subject to recall bias. Additionally, this scale incorporates objective and subjective criteria but defines neither. This endpoint will not be reviewed.*

Global Assessment of Improvement (As Per Subject)—for the whole scalp

Score	Category
5	Clear
4	Almost clear
3	Marked improvement
2	Moderate improvement
1	Minimal improvement
0	No change
-1	Worse

Source: Sponsor's NDA submission vol 1.39 p.6923

Reviewer's Comment: *The endpoint Global Assessment of Improvement per Subject used a dynamic scale that lacks definition. Dynamic scales are subject to recall bias, and differing values and category interpretations among subjects complicate self-assessments. The Sponsor has not submitted evidence regarding the validation of this instrument. This endpoint will not be reviewed.*

Results

A total of 148 subjects from 12 study centers were enrolled and randomized into the study to receive either Clobetasol Propionate Shampoo, 0.05% or Clobetasol Propionate Shampoo Vehicle. Enrollment exceeded protocol specifications as 16 subjects were enrolled and randomized prior to notification that target enrollment had been achieved. Table 15 shows the subject disposition.

Table 15: Disposition of Study Subjects, Study RD.06.SRE.18076

Disposition	Clobetasol Propionate Shampoo, 0.05% N=95	Clobetasol Propionate Shampoo Vehicle N=47	Total N=142
Enrolled	95 (100)	47 (100)	142 (100)
Randomized	95 (100)	47 (100)	142 (100)
ITT population	95 (100)	47 (100)	142 (100)
PP population	84 (88.4)	42 (89.4)	126 (88.7)

Safety population	94 (98.9)	47 (100)	141 (99.3)
Completed study	88 (92.6)	44 (93.6)	132 (93.0)
Discontinued	7 (7.4)	3 (6.4)	10 (7.0)
Lack of efficacy	0 (0)	0 (0)	0 (0)
Adverse event	1 (1.1)	0 (0)	1 (0.7)
Subject request	3 (3.2)	2 (4.3)	5 (3.5)
Protocol violation	2 (2.1)	1 (2.1)	3 (2.1)
Lost to follow-up	1 (1.1)	0 (0)	1 (0.7)

Source: Sponsor's NDA submission, vol 1.39, p. 6715

Among the 142 randomized subjects, 16 were found to have violated the protocol after receiving study medication and were not included in the PP (per protocol) population. Reasons included not meeting inclusion/exclusion criteria (2 active and 1 vehicle subject/s), missing 2 or more visits (2 active subjects), missing doses for 5 or more consecutive days (1 active and 2 vehicle subject/s), receiving prohibited concomitant medication (4 active and 1 vehicle subject/s), no ost-baseline data (1 active and 1 vehicle subject), and being discontinued from the study due to protocol violation per Investigator's judgment (1 active subject). Hence 126 subjects were included in the Per Protocol population.

Reviewer's Comment: *The Division and Sponsor agreed that the primary endpoint would be assessed for the intent-to-treat (ITT) population. The review will focus on the ITT population.*

Patient demographics are outlined in Table 16.

Table 16: Demographic Characteristics of Study Subjects, ITT Population,Study 18076

Demographic Parameter	**Clobetasol** Propionate **Shampoo 0.05% N=95 5**	**Clobebetasol Propionate Shampoo Vehicle N=47**	**Total N=142**	**p-value**
Gender				
Male	38 (40.0)	22 (46.8)	60 (42.3)	0.419
Female	57 (60.0)	25 (53.2)	82 (57.7)	
Race				
Caucasian	88 (92.6)	43 (91.5)	131 (92.3)	
Black	2 (2.1)	1 (2.1)	3 (2.1)	0.863
Asian	0 (0)	0 (0)	0 (0)	
Hispanic	4 (4.2)	3 (6.4)	7 (4.9)	
Other	1 (1.1)	0 (0)	1 (0.7)	
Age (mean)	45.1	45.1	45.1	0.887
Age ranges (yrs)				
12 to 17 years	2 (2.1)	2 (4.3)	4 (2.8)	
18 to 64 years	82 (86.3)	39 (83.0)	121 (85.2)	0.807
≥65 years	11 (11.6)	6 (12.8)	17 (12.0)	

Source: Sponsor's NDA submission, vol. 1.39 p.6718.

Reviewer's Comment: *Age, race and gender appear to be comparably distributed between the active and vehicle groups.*

Baseline disease severity is outlined in Table 17

Table 17:Global Severity at Baseline

Global Severity Score *descriptor (numeric score)*	**Clobetasol** Propionate **Shampoo 0.05% N=99** *n(%)*	**Clobebetasol Propionate Shampoo Vehicle N=49** *n(%)*	**p-value**
Moderate (3)	70 (73.7)	32 (68.1)	0.486
Severe (4)	20 (21.1)	10 (21.3)	
Very Severe (5)	5 (5.3)	5 (10.6)	

Source: Sponsor's NDA submission, vol. 1.39, and p.6723.

Reviewer's Comment: *Baseline disease severity as measured by the Global Severity Scale was similar for both study arms. The majority of patients had moderate disease.*

Efficacy Endpoint Outcomes

The results of the primary efficacy variable, success in Global Severity at the week 4 endpoint, are presented in Table 18.

Table 18: Number of Patients with Success in Global Severity at Week 4,Study 18075

Population	Clobetasol Propionate Shampoo, 0.05% n/N(%)	Clobetasol Propionate Shampoo Vehicle n/N(%)	p-value
ITT	40/91 (44.0%)	1/45 (2.2%)	<0.001
ITT (LOCF)	**40/95 (42.1%)**	**1/47 (2.1%)**	**<0.001**
PP	39/84 (46.4%)	1/42 (2.4%)	<0.001
PP (LOCF)	39/84 (46.4%)	1/42 (2.4%)	<0.001

Source: Sponsor'NDA submission, Vol. 1.39, pp.6784-5.

N=total number of evaluable subjects at week 4
n=number of subjects with success
ITT=intent to treat
PP=per protocol
LOCF=last observation carried forward

The results of the relevant secondary efficacy variables are delineated in table 19.

Table 19: Secondary Efficacy Variables at Week 4 Endpoint, ITT Population (LOCF), Study 18076

Variable	Clobetasol Propionate Shampoo, 0.05% N=95	Clobetasol Propionate Shampoo Vehicle N=47	p-value
Erythema: none or mild n(%)	65 (68.4)	16 (34.0)	0.0001
Scaling: none n(%)	21 (22.1)	0 (0)	0.0006

Plaque thickening: none n(%)	35 (36.8)	5 (10.6)	0.0015
Pruritus: none n(%)	43 (45.3)	6 (12.8)	0.0002

Source: Sponsor's NDA submission, vol. 1.39 pp.6725, 6727, and FDA Biostatistician's analysis.

Reviewer's Comment: *In the pivotal trial Study **18076**, Clobetasol Shampoo was superior to its vehicle for the primary efficacy endpoint success in global severity for the ITT (LOCF) population (p-value <0.001); this also held true for the PP (LOCF) population (p-value <0.001). The secondary endpoints were supportive in that proportion of subjects who achieved success for erythema, scaling and plaque thickening were significantly greater in the Clobetasol Shampoo arm than the vehicle shampoo arm (p-values of <0.001 for all). Additionally, the proportion of sujbects with resolution of pruritus was significantly greater in the active versus the vehicle arms (p-value <0.001).*

Non-pivotal Trials for Scalp Psoriasis

Non-pivotal Study #1: Protocol Number RD.03.SPR.**2638**

Title: Parallel group comparison of 4-week treatment with Clobetasol 17-propionate 0.05% Shampoo versus Calcipotriol solution 0.005% (Dovonex/Daivonex™) – An efficacy and safety study in subjects with scalp psoriasis

Reviewer's Comment: *This European study is considered non-pivotal as it is not vehicle-controlled and therefore can only provide comparative efficacy information.*

Investigator	Site Number, Country	N (clobetasol/calcipotriol/total)
⌜	⌝	10/10/20
		10/10/20
		8/8/16
		4/4/8
		4/4/8
		6/6/12
		4/4/8
		8/8/16
		6/6/12
		4/3/7
		2/3/5
		4/4/8
⌞	⌟	2/1/3
		4/4/8

Source: Sponsor's NDA submission, vol 1.43, p.8481

Reviewer's comment*: Enrollment at some sites was low.*

Objective/Rationale

The objectives of the study were to compare the efficacy and safety of Clobetasol Propionate Shampoo, 0.05% and calcipotriol 0.005% solution (Dovonex/Daivonex™) in subjects with moderate to severe scalp psoriasis, and to show the non-inferiority and/or superiority in efficacy of clobetasol versus the comparator product.

Overall Study Design

This study was a randomized, multi-center, investigator-blinded, active-controlled comparison of two parallel groups. One hundred and fifty-one subjects ages 12 years or older who met specific enrollment criteria were randomized in a 1:1 ratio to receive either Clobetasol Propionate Shampoo, 0.05% once daily or Daivonex™ solution twice daily for 4 weeks. Subjects were evaluated at baseline and weeks 2 and 4.

Reviewer's Comment: *Because of the difference in the appearance, dosage form and dosing schedule between Clobetasol Propionate Shampoo, 0.05% and Daivonex™ solution, the study subjects were aware of which treatment they received and only the evaluating investigator was blinded.*

Inclusion Criteria

The inclusion criteria for this study were the same as for the pivotal trials except for an additional requirement in this study for at least 2 cm^2 of scalp involvement (no requirement for size of involved scalp in the pivotal studies).

Exclusion Criteria

The exclusion criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that the washout periods for systemic anti-psoriatic treatments was 4 weeks rather than 6, 8, or 16 weeks in the pivotal trials (for PUVA, systemic immunosuppressants and systemic retinoids, respectively).

Reviewer's Comment: *The shorter washout period in this study may have resulted in prior systemic treatments exerting residual effect on the disease process. However, the predicted effect would be to blunt the observed treatment effect, and randomization should have ensured equal impact in both treatment groups.*

Withdrawal Criteria

Withdrawal criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that clearance before the end of the study (week 4) was a reason for withdrawal in this study.

Procedures and Observations

Subjects in the clobetasol propionate group were provided with two 100-gram tubes of study drug every two weeks. They were instructed to apply their usual quantity of shampoo to dry scalp, then lather and rinse after 15 minutes. Subjects in the Daivonex™ group were provided with two 60-mL bottles of study drug every two weeks. They were instructed to comb hair to remove scaly debris then apply Daivonex™ solution to affected scalp areas twice daily. Safety and efficacy measurements were taken at baseline, week 2 and week 4.

Efficacy Endpoints

The primary efficacy endpoints specified in the protocol are Global Severity Score and Total Symptom Score. The Global Severity Score utilizes a static 6-point investigator's global assessment scale (Table 20, below). Total Severity Score is the sum of the individual scores for erythema, scaling and plaque thickening.

Table 20: Global Severity Scale

None	0	No clinical signs or symptoms detected.
Very mild	1	Only very slight signs or symptoms detected (e.g., very fine scaling or slight erythema)
Mild	2	Slight signs or symptoms detected (e.g. mild erythema and scaling, eventually associated to some barely detectable plaque elevation).
Moderate	3	Moderate, clearly detectable signs or symptoms (e.g., definite redness with obvious scaling on a plaque that often was elevated above skin level).
Severe	4	Severe signs or symptoms detected (e.g., intense redness, profuse shedding and definite plaque thickness were most often all present).
Very Severe	5	Very severe signs or symptoms detected (e.g., maximum erythema with heavy scale production. On highly elevated plaque; in some acute phase; pustules were seen).

Reviewer's Comments: *The Global Severity Scale is a static investigator's global scale that is qualitatively very similar to the Global Severity Scale used in the two pivotal trials,* ***18075*** *and* ***18076****. However, the scale descriptions are worded slightly differently in this study. Additionally, the Global Severity Scale is not dichotomized to success and failure in this non-pivotal study, as it was in the pivotal trials.*

The Total Severity Score is a computed score that is not in routine clinical use in the United States. Because it lacks clinical relevance, it was not used as a primary efficacy endpoint in the pivotal trials.

Secondary efficacy endpoints specified in the protocol include erythema, scaling/desquamation, plaque thickening, pruritus, investigator's global assessment of improvement (dynamic) and subject's global assessment of improvement (dynamic). The scales for Total Severity Score and all of the secondary efficacy endpoints are the same as those in pivotal studies **18075** and **18076**.

Reviewer's Comment: *Erythema, scaling/desquamation and plaque thickening have typically been accepted by the Division as acceptable secondary endpoints, and were similarly assessed in the pivotal trials; these endpoints will be briefly reviewed for this study. The subject's global*

assessment of improvement may be biased, as the subjects were not blinded to their treatment. Dynamic scales, such as the investigator's global assessment of improvement and the subject's global assessment of improvement, are subject to recall bias.

Results

One hundred and fifty-one subjects from 14 centers across Europe were randomized into the study. Tables 21-23 show the subjects disposition, demographics and baseline severity scores.

Table 21: Disposition of Study Subjects

	Group					
	Clobetasol (N=76)		Calcipotriol (N=75)		Total (N=151)	
	N	%	N	%	N	%
Eligible	76	100.0	75	100.0	151	100.0
ITT population	76	100.0	75	100.0	151	100.0
Major deviators	9	11.8	14	18.7	23	15.2
Per protocol (PP)	67	88.2	61	81.3	128	84.8

Source: Sponsor's NDA submission, vol. 1.43, p 8175.

Table 22: Demographic Characteristics, ITT Population

	Clobetasol group	Calcipotriol group
Age (mean)	44.86	45.67
Gender N (%)		
Male	37 (48.7)	34 (45.3)
Female	39 (51.3)	41 (54.7)
Race N (%)		
White	75 (98.7)	74 (98.7)
Black	1 (1.3)	1 (1.3)

Source: Sponsor's NDA submission, vol 1.43, p8168.

Reviewer's Comment: *Age, race and gender appear to be comparably distributed between the two treatment groups. The preponderance of subjects of white race does not replicate the racial and ethnic diversity of the US population.*

Table 23: Baseline Assessments

	Clobetasol group (mean ± SD)	Calcipotriol group (mean ± SD)
Global Severity Score (0-5)	3.49±0.60	3.51±0.60
Total Severity Score (0-9)	4.86±1.95	4.95±1.49

Source: Sponsor's NDA submission, vol. 1.43, p8169.

Reviewer's Comment: *The baseline scores for the primary efficacy variables, Global Severity Score and Total Severity Score, appear to be comparable between the two treatment groups.*

Efficacy Endpoint Outcomes

Table 24: Total Severity Score, Summary Statistics by Visit

		Group		
		Clobetasol Propionate Shampoo, 0.05%	Calcipotriol	Total
ITT(LOCF)				
Baseline	N	76	75	151
	Mean (SD)	4.86 (1.95)	4.95 (1.49)	4.90 (1.73)
Week 4	N	76	75	151
	Mean (SD)	1.76 (1.57)	2.36 (1.64)	2.06 (1.62)
PP				
Baseline	N	67	61	128
	Mean (SD)	4.82 (1.97)	4.99 (1.53)	4.90 (1.77)
Week 4	N	67	61	128
	Mean (SD)	1.64 (1.49)	1.94 (1.35)	1.78 (1.43)

Source: Sponsor's NDA submission, vol 1.43, pp.8503, 8513.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) did not suggest an interaction, therefore the model without interaction was used in the table below (Table 25).

Table 25: Total Severity Score, Estimated Difference (Clobetasol-Calcipotriol), Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Estim. Diff.	SE	95% CI	p-Value
W/o inter. TreatXcenter ITT(LOCF)	Week 4	-0.51	0.23	-0.97, -0.05	0.028
W/o inter. TreatXcenter PP	Week 4	-0.24	0.21	-0.66, 0.18	0.267

Source: Sponsor's NDA submission, vol 1.43, pp.8503, 8513.

The difference in the reduction in TSS from baseline to week 4 between the clobetasol and calcipotriol treatment groups was significant for the ITT but not the PP populations. The Sponsor attributed this discrepancy to the fact that more subjects were excluded from the PP population in the clobetasol propionate group (N=14, 18.7%) than the calcipotriol group (N=9, 11.8%), and that excluded clobetasol propionate subjects had lower TSS than those that were not excluded. The statistical analysis plan in the protocol prespecified that non-inferiority would be achieved if the upper limit of the confidence interval was below the target delta of 1.5 for TSS in the PP population; it was 0.18. The Sponsor concluded that Clobetasol Propionate Shampoo, 0.05% is non-inferior to Daivonex™ solution.

Reviewer's Comments: *Non-inferiority of Clobetasol Propionate Shampoo, 0.05% relative to Daivonex™ Solution was demonstrated by the criteria prespecified in the protocol statistical analysis plan, but the lack of blinding of subjects between the Clobetasol Propionate Shampoo, 0.05% and Daivonex™ Solution treatment groups may have introduced bias. The large delta for non-inferiority (1.5) is also a weakness of this study. Finally, treatment effect occurs later with the comparator drug, calcipotriol, than with corticosteroids; the relatively early endpoint (4 weeks) favors clobetasol propionate.*

Table 26: Global Severity Score, Summary Statistics by Visit

		Group		
		Clobetasol Propionate Shampoo, 0.05%	Calciptriol	Total
ITT(LOCF)				
Baseline	N	76	75	151
	Mean (SD)	3.49 (0.60)	3.51 (0.60)	3.50 (0.60)
Week 4	N	76	75	151
	Mean (SD)	1.55 (1.20)	2.03 (1.31)	1.79 (1.28)
PP				
Baseline	N	67	61	128
	Mean (SD)	3.42 (0.55)	3.51 (0.62)	3.46 (0.59)
Week 4	N	67	61	128
	Mean (SD)	1.42 (1.09)	1.74 (1.17)	1.57 (1.13)

Source: Sponsor's NDA submission, vol 1.43, pp.8523, 8533.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) did not suggest an interaction, therefore the model without interaction was used in the table below (Table 27).

Table 27: Global Severity Score, Estimated Difference (Clobetasol-Calcipotriol), Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Estimated Difference	SE	95% CI	p-Value
W/o inter. TreatXcenter ITT(LOCF)	Week 4	-0.67	0.15	-0.96, -0.38	<0.001
W/o inter. TreatXcenter PP	Week 4	-0.27	0.17	-0.59, 0.06	0.114

Source: Sponsor's NDA submission, vol 1.43, pp.8523, 8533.

The difference in the reduction in GSS from baseline to week 4 between the clobetasol and calcipotriol treatment groups was significant for the ITT but not the PP populations. The Sponsor again attributed this discrepancy to the fact that more subjects were excluded from the PP population in the clobetasol propionate group (N=14, 18.7%) than the calcipotriol group (N=9, 11.8%), and that excluded clobetasol propionate subjects had lower GSS than those that were not excluded. The statistical analysis plan in the protocol prespecified that superiority would be

achieved if a significant difference in favor of clobetasol propionate was detected in both primary efficacy criteria, TSS and GSS, for the ITT population. The difference favored Clobetasol Propionate Shampoo, 0.05% and was significant for both TSS ($p=0.028$) and GSS ($p \leq 0.001$) in the ITT(LOCF) population. The Sponsor concluded that Clobetasol Propionate Shampoo, 0.05% is superior to Daivonex™ solution for the endpoints described.

Reviewer's Comments: *Superiority of Clobetasol Propionate Shampoo, 0.05% relative to Daivonex™ Solution was demonstrated by the criteria pre-specified in the protocol statistical analysis plan. The lack of subject blinding between the Clobetasol Propionate Shampoo, 0.05% and Daivonex™ Solution treatment groups may have introduced bias. The use of a comparator drug rather than vehicle is also a weakness of this study. Finally, maximal treatment effect of calcipotriol is achieved later than 4 weeks, thus the timepoint for evaluation favors clobetasol propionate.*

The secondary endpoints of erythema, scaling/desquamation and plaque thickening decreased in both the Clobetasol Propionate Shampoo, 0.05% and the Daivonex™ solution groups, for both the ITT(LOCF) and PP populations. The decrease was generally larger in the Clobetasol Propionate Shampoo, 0.05% group.

Reviewer's Comments: *Although study **2638** demonstrated non-inferiority and superiority of Clobetasol Propionate Shampoo, 0.05% relative to Daivonex™ Solution by the criteria pre-specified in the protocol statistical analysis plan, the weaknesses described above are significant. The study does not contradict the efficacy demonstrated in the pivotal trials (**18075** and **18076**) of Clobetasol Propionate Shampoo, 0.05%, it but adds little.*

Non-pivotal Study #2: Protocol Number RD.03.SPR.**2648**

Title: The Safety and Efficacy of Clobetasol Propionate Shampoo, 0.05% compared to Polytar Liquid® in the treatment of scalp psoriasis

Reviewer's Comment: *This British study is considered non-pivotal as it is not vehicle-controlled and therefore can only provide comparative efficacy information.*

Investigator	Site Number, Country	Psuedocenter (northern/southern)
[redacted]	[redacted]	N
		S
		N
		S
		N
		N
		S
		N
		S
		S
		N

[redacted]	N
	N
	N
	S
	N
	N
	N
	S
	S
	S

Source: Sponsor's NDA submission vol. 1.46, pp.9092-5.

***Reviewer's comment**: Enrollment per site ranged from 1 to 18 subjects. Because enrollment in some sites was low, the sites were grouped for analysis into two psuedocenters, northern and southern.*

Objective/Rationale

The study objectives were to compare the efficacy of Clobetasol Propionate Shampoo, 0.05% versus the marketed topical product Polytar Liquid® in subjects with moderate to severe scalp psoriasis, and to provide safety data to support the registration of the drug on a worldwide basis.

Overall Study Design

This study was randomized, multi-center, investigator-blinded, parallel group, and active-controlled. One hundred and sixty-two subjects ages 18 years or older who met specific enrollment criteria were randomized in a 3:1 ratio to receive either Clobetasol Propionate Shampoo, 0.05% once daily or Polytar Liquid® twice weekly for 4 weeks. Subjects were evaluated at baseline and weeks 2 and 4.

***Reviewer's Comment:** Because of the difference in the appearance and dosing schedule between Clobetasol Propionate Shampoo, 0.05% and Polytar Liquid®, only the evaluating investigator, not the study subjects, was blinded.*

Inclusion Criteria

The inclusion criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except for an additional requirement in this study for involvement of at least 15% of scalp surface area (no requirement for percent surface area of involved scalp in the pivotal studies).

Exclusion Criteria

The exclusion criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that the wash-out periods for systemic anti-psoriatic treatments was 4 weeks

rather than 6, 8, or 16 weeks in the pivotal trials (for PUVA, systemic immunosuppressants and systemic retinoids, respectively).

Reviewer's Comment: *The shorter washout period in this study may have resulted in prior systemic treatments exerting residual effect on the disease process. However, the predicted effect would be to blunt the observed treatment effect, and randomization should have ensured equal impact in both treatment groups.*

Withdrawal Criteria

Withdrawal criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that clearance before the end of the study (week 4) was a reason for withdrawal in this study.

Procedures and Observations

Subjects in the clobetasol propionate group were provided with two 100-gram tubes of study drug every two weeks. They were instructed to apply their usual quantity of shampoo to dry scalp, massage into the lesions, then lather and rinse after 15 minutes. Subjects in the Polytar Liquid® group were provided with two 150-mL bottles of study drug every two weeks. They were instructed to apply their usual quantity of shampoo to wet scalp, massage into the lesions, then lather and rinse. Subjects were permitted to use a cosmetic shampoo if desired on the days that Polytar Liquid® was not used. Safety and efficacy measurements were taken at baseline, week 2 and week 4.

Efficacy Endpoints

The primary efficacy endpoints specified in the protocol are Global Severity Score and Total Symptom Score. The Global Severity Score, a static 6-point investigator's global assessment scale, is identical to the Global Severity Scale used in the non-pivotal study RD.03.SPR.**2638**. Total Severity Score is the sum of the individual scores for erythema, scaling and plaque thickening.

Reviewer's Comments: *As in study RD.03.SPR.**2638**, the Global Severity Scale is a static investigator's global scale that is qualitatively very similar to the Global Severity Scale used in the two pivotal trials, **18075** and **18076**. However, the Global Severity Scale is not dichotomized to success and failure in this non-pivotal study, as it was in the pivotal trials.*

The Total Severity Score is a computed score that is not in routine clinical use in the United States. Because it lacks clinical relevance, it was not used as a primary efficacy endpoint in the pivotal trials.

Secondary efficacy endpoints specified in the protocol include erythema, scaling/desquamation, plaque thickening, pruritus, investigator's global assessment of improvement (dynamic) and subject's global assessment of improvement (dynamic). The scales for Total Severity Score and all of the secondary efficacy endpoints are the same as those in pivotal studies **18075** and **18076**.

Reviewer's Comment: *Erythema, scaling/desquamation and plaque thickening have typically been accepted by the Division as acceptable secondary endpoints in psoriasis studies and were similarly assessed in the pivotal trials; these endpoints will be briefly reviewed. The subject's global assessment of improvement may be biased, as the subjects were not blinded to their treatment. Dynamic scales, such as the investigator's global assessment of improvement and the subject's global assessment of improvement, are subject to recall bias.*

Results

One hundred and sixty-two subjects from 21 centers in Great Britain were randomized into the study. Tables 28-30 show the subjects disposition, demographics and baseline severity scores.

Table 28: Disposition of Study Subjects

	Group		
	Clobetasol	Polytar Liquid®	Total
Eligible	121	41	162
ITT population	121	41	162
Per protocol (PP)	105	32	137

Source: Sponsor's NDA submission, vol. 1.46, p9177.

Table 29: Demographic Characteristics, ITT Population

	Clobetasol group	Polytar Liquid® group
Age (mean)	46.7	45.4
Gender N (%)		
Male	59 (48.8)	27 (65.9)
Female	62 (51.2)	14 (34.1)
Race N (%)		
White	116 (95.9)	38 (92.7)
Black	1 (0.8)	2 (4.9)
Asian	2 (1.7)	0 (0.0)
Mixed	2 (1.7)	1 (2.4)

Source: Sponsor's NDA submission, vol 1.46, p9125.

Reviewer's Comment: *Subject age appears to be comparable between the two treatment groups. Both genders were approximately equally represented in the Clobetasol Propionate Shampoo, 0.05% group, but the Polytar Liquid® group contains a higher proportion of males. Additionally, the Polytar Liquid® group has a higher proportion of non-white subjects.*

Table 30: Baseline Assessments

	Clobetasol group (mean ± SD)	Polytar Liquid® group (mean ± SD)
Global Severity Score (0-5)	3.4±0.6	3.5±0.6
Total Severity Score (0-9)	6.1±1.4	6.3±1.2

Source: Sponsor's NDA submission, vol. 1.46, p9128.

Reviewer's Comment: *The baseline scores for the primary efficacy endpoints, Global Severity Score and Total Severity Score, appear to be comparable between the two treatment groups.*

Efficacy Endpoint Outcomes

Table 31: Total Severity Score, Summary Statistics by Visit

		Group		
		Clobetasol Propionate Shampoo, 0.05%	Polytar Liquid	Total
ITT(LOCF)				
Baseline	N	121	41	162
	Mean (SD)	6.3 (1.4)	6.3 (1.2)	6.1 (1.4)
Week 4	N	121	41	162
	Mean (SD)	3.2 (2.0)	5.2 (1.9)	3.7 (2.2)
PP				
Baseline	N	105	32	137
	Mean (SD)	6.1 (1.3)	6.2 (1.2)	6.1 (1.3)
Week 4	N	105	32	137
	Mean (SD)	3.1 (1.9)	5.3 (1.9)	3.6 (2.1)

Source: Sponsor's NDA submission, vol 1.46, pp.9214, 9230.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) did not suggest an interaction, therefore the model without interaction was used in the table below (Table 32).

Table 32: Total Severity Score, Estimated Difference (Clobetasol-Polytar), Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Estim. Diff.	SE	95% CI	p-Value
W/o inter. TreatXcenter ITT(LOCF)	Week 4	-1.842	0.321	-1.914, -0.777	0.0001
W/o inter. TreatXcenter PP	Week 4	-2.066	0.334	-2.727, -1.405	0.0001

Source: Sponsor's NDA submission, vol 1.46, pp.9219, 9235.

The difference in the reduction in TSS from baseline to week 4 between the clobetasol propionate shampoo and the Polytar Liquid® treatment groups was significant for both the ITT(LOCF) and the PP populations. The statistical analysis plan in the protocol pre-specified that non-inferiority would be achieved if the upper limit of the confidence interval was below the target delta of 1.5 for TSS in the PP population; it was –1.405. The Sponsor concluded that Clobetasol Propionate Shampoo, 0.05% is non-inferior to Polytar Liquid®.

Reviewer's Comments: *Non-inferiority of Clobetasol Propionate Shampoo, 0.05% relative to Polytar Liquid® was demonstrated by the criteria pre-specified in the protocol statistical analysis plan. However, the large delta for non-inferiority (1.5) and the potential bias introduced by the lack of subject blinding to treatment are weaknesses of this study and decrease the utility of this study.*

Table 33: Global Severity Score, Summary Statistics by Visit

		Group		
		Clobetasol Propionate Shampoo, 0.05%	Polytar Liquid	Total
ITT(LOCF)				
Baseline	N	121	41	162
	Mean (SD)	3.4 (0.6)	3.5 (0.6)	3.4 (0.6)
Week 4	N	121	41	162
	Mean (SD)	1.9 (1.0)	3.0 (1.0)	2.2 (1.1)
PP				
Baseline	N	105	32	137
	Mean (SD)	3.4 (0.6)	3.4 (0.6)	3.4 (0.6)
Week 4	N	105	32	137
	Mean (SD)	1.9 (1.0)	3.0 (1.0)	2.2 (1.1)

Source: Sponsor's NDA submission, vol 1.46, pp.9246, 9261.

Analysis of covariance for treatment comparison with and without interaction (treatmentXcenter) did not suggest an interaction, therefore the model without interaction was used in the table below (Table 34).

Table 34: Global Severity Score, Estimated Difference (Clobetasol-Polytar), Analysis of Covariance for Treatment Comparison

ANCOVA: Model	Visit	Estim. Diff.	SE	95% CI	p-Value
W/o inter. TreatXcenter ITT(LOCF)	Week 4	-1.010	0.176	-1.357, -0.663	0.0001
W/o inter. TreatXcenter PP	Week 4	-1.126	0.186	-1.494, -0.758	0.0001

Source: Sponsor's NDA submission, vol 1.46, pp.9251, 9266.

The difference in the reduction in GSS from baseline to week 4 between the clobetasol propionate shampoo and the Polytar Liquid® treatment groups was significant for both the ITT(LOCF) and the PP populations. The statistical analysis plan in the protocol prespecified that superiority would be achieved if a significant difference in favor of clobetasol propionate was

detected in both primary efficacy criteria, TSS and GSS, for the ITT population. This was achieved.

Reviewer's Comments: *Superiority of Clobetasol Propionate Shampoo, 0.05% to Polytar Liquid® was demonstrated by the criteria prespecified in the protocol statistical analysis plan. However, the lack of blinding between treatment groups and the use of a comparator drug rather than vehicle are weaknesses of this study.*

The secondary endpoints of erythema, scaling/desquamation and plaque thickening decreased in both the Clobetasol Propionate Shampoo, 0.05% and the Polytar Liquid® groups, for both the ITT(LOCF) and PP populations. The decrease was significantly larger in the Clobetasol Propionate Shampoo, 0.05% group, for both the ITT(LOCF) and the PP populations. The results for the ITT(LOCF) population are included in the table below.

Table 35: Secondary Efficacy Variables at Baseline and Week 4

Efficacy variable score Mean ± SD	Timepoint	Clobetasol Shampoo N=121	Polytar Liquid® N=41	P-value
Erythema (scale 0 – 3)	Baseline	1.9±0.6	1.9±0.6	0.0001
	Week 4	1.2±0.8	1.7±0.7	
Plaque thickening (scale 0 – 3)	Baseline	2.0±0.7	2.1±0.6	0.0001
	Week 4	0.9±0.8	1.6±0.9	
Desquamation (scale 0 – 3)	Baseline	2.2±0.6	2.3±0.5	0.0001
	Week 4	1.1±0.8	1.9±0.8	
Pruritus (scale 0 – 3)	Baseline	1.7±0.9	1.7±0.8	0.0002
	Week 4	0.6±0.8	1.2±0.8	

Source: Sponsor's NDA submission vol.1.46, p.9153.

Reviewer's Comments: *Although study **2648** demonstrated non-inferiority and superiority of Clobetasol Propionate Shampoo, 0.05% relative to Polytar Liquid® by the criteria pre-specified in the protocol statistical analysis plan, the weaknesses described above are significant. The study does not contradict the efficacy demonstrated in the pivotal trials (**18075** and **18076**) of Clobetasol Propionate Shampoo, 0.05%, it but adds little.*

Non-pivotal Study #3: Protocol Number RD.03.SPR.**2665**

Title: Efficacy and Safety of Clobetasol Propionate Shampoo, 0.05% as Compared to its Vehicle and Clobetasol Propionate 0.05% Gel (Dermoval™ Gel) in the Treatment of Subjects with Scalp Psoriasis

Reviewer's Comment: *This European study is considered non-pivotal as Dermoval™ gel is not marketed in the U.S.*

Investigator	Site Number, Country	N (clobetasol shampoo/Dermoval/vehicle)
[redacted]	[redacted]	2/2/0
		6/4/2
		3/3/1
		3/3/1
		3/3/0

4/5/2
6/4/1
9/9/3
7/7/3
6/6/2
6/6/2
6/6/2
3/3/1

Source: Sponsor's NDA submission, vol. 1.49, p.10444.

***Reviewer's comment**: Because enrollment at some sites was low Enrollment per site ranged from 4 to 21 subjects. Because enrollment in most of the French sites was low, the French sites were grouped into two psuedocenters for statistical analysis.*

Objective/Rationale

The study objectives were to demonstrate the non-inferior efficacy of Clobetasol Propionate Shampoo, 0.05% versus Dermoval™ Gel and superior efficacy of Clobetasol Propionate Shampoo, 0.05% versus Vehicle Shampoo, and to provide safety data to support the registration of the drug on a worldwide basis.

***Reviewer's Comment:** Although Dermoval™ Gel is not approved for marketing in the US, the demonstration of non-inferiority of Clobetasol Propionate Shampoo, 0.05% to another clobetasol propionate dosage form in a study of robust design would be supportive evidence of efficacy.*

Overall Study Design

This study was randomized, multi-center, investigator-blinded, parallel-group, and active- and vehicle-controlled. One hundred and forty subjects ages 18 years or older who met specific enrollment criteria were randomized in a 3:3:1 ratio to receive either Clobetasol Propionate Shampoo, 0.05%, Dermoval™ Gel or Vehicle Shampoo once daily for 4 weeks. Subjects were evaluated at baseline and weeks 2 and 4.

***Reviewer's Comment:** Because of the difference in the appearance and dosing schedule between Clobetasol Propionate Shampoo, 0.05% and Dermoval™ gel, only the evaluating investigator, not the study subjects, was fully blinded. The study subjects in the Clobetasol Propionate Shampoo, 0.05% and Vehicle Shampoo groups were partially blinded, but they were not blinded relative to Dermoval™ Gel, and the Dermoval™ Gel subjects were not blinded at all.*

Inclusion Criteria

The inclusion criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except for an additional requirement in this study for involvement of at least 15% of scalp surface area (no requirement for percent surface area of involved scalp in the pivotal studies).

Exclusion Criteria

The exclusion criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that the wash-out periods for systemic anti-psoriatic treatments was 4 weeks rather than 6, 8, or 16 weeks in the pivotal trials (for PUVA, systemic immunosuppressants and systemic retinoids, respectively).

Reviewer's Comment: *The shorter washout period in this study may have resulted in prior systemic treatments exerting residual effect on the disease process. However, the predicted effect would be to blunt the observed treatment effect, and randomization should have ensured equal impact in all treatment groups.*

Withdrawal Criteria

Withdrawal criteria for this study were the same as for the pivotal trials (studies **18075** and **18076**) except that clearance before the end of the study (week 4) was a reason for withdrawal in this study.

Procedures and Observations

Subjects in the clobetasol propionate shampoo group and vehicle shampoo group were provided with one 120-gram bottle of study drug every two weeks. They were instructed to apply their usual quantity of shampoo to dry scalp, massage into the lesions, then lather and rinse after 15 minutes. Subjects in the Dermoval™ Gel group were provided with six 20ml tubes of study drug every two weeks. They were instructed to apply study drug to dry scalp once daily, not to exceed 50gm per week.. Safety and efficacy measurements were taken at baseline, week 2 and week 4.

Efficacy Endpoints

The primary efficacy endpoints specified in the protocol are Global Severity Score and Total Symptom Score. The Global Severity Score, a static 6-point investigator's global assessment scale, is identical to the Global Severity Scale used in the non-pivotal study RD.03.SPR.**2638**. Total Severity Score is the sum of the individual scores for erythema, scaling and plaque thickening.

Reviewer's Comments: *As in studies RD.03.SPR.**2638** and RD.03.SPR.**2648**, the Global Severity Scale is a static investigator's global scale that is qualitatively very similar to the Global Severity Scale used in the two pivotal trials, **18075** and **18076**. However, the Global Severity Scale is not dichotomized to success and failure in this non-pivotal study, as it was in the pivotal trials.*

The Total Severity Score is a computed score that is not in routine clinical use in the United States. Because it lacks clinical relevance, it was not used as a primary efficacy endpoint in the pivotal trials.

Secondary efficacy endpoints specified in the protocol include erythema, scaling/desquamation, plaque thickening, pruritus, investigator's global assessment of improvement (dynamic) and subject's global assessment of improvement (dynamic). The scales for Total Severity Score and all of the secondary efficacy endpoints are the same as those in pivotal studies **18075** and **18076**.

Reviewer's Comment: *Erythema, scaling/desquamation and plaque thickening have typically been accepted by the Division as acceptable secondary endpoints in psoriasis studies and were similarly assessed in the pivotal trials; these endpoints will be briefly reviewed. The subject's global assessment of improvement may be biased, as the subjects were not blinded to their treatment. Dynamic scales, such as the investigator's global assessment of improvement and the subject's global assessment of improvement, are subject to recall bias.*

Results

One hundred and forty-four subjects from 13 centers across Europe were randomized into the study. Tables 36-38 show the subjects disposition, demographics and baseline severity scores.

Table 36: Disposition of Study Subjects

	Group			
	Clobetasol Shampoo	Dermoval™ Gel	Vehicle Shampoo	Total
Eligible	63 (100%)	61 (100%)	20 (100%)	144 (100%)
ITT population	63 (100%)	61 (100%)	20 (100%)	144 (100%)
Per protocol (PP)	57 (90.5%)	55 (90.2%)	16 (80.0%)	128 (88.9%)

Source: Sponsor's NDA submission, vol. 1.49, p10444.

Table 37: Demographic Characteristics, ITT Population

	Clobetasol Shampoo	Dermoval™ Gel	Vehicle Shampoo
Age (mean)	43.9	50.6	47.5
Gender N (%)			
Male	35 (55.6)	23 (37.7)	10 (50.0)
Female	28 (44.4)	38 (62.3)	10 (50.0)
Race N (%)			
White	63 (100)	60 (98.4)	20 (100)
Black	0 (0)	1 (1.6)	0 (0)

Source: Sponsor's NDA submission, vol 1.49, p10407.

Reviewer's Comment: *Mean age for the three groups falls within a 10-year bracket. Both genders were equally represented in the Vehicle Shampoo group, but the Dermoval™ gel group contains a higher proportion of females and the Clobetasol Propionate Shampoo, 0.05% group a higher proportion of males. The study subjects were almost exclusively white; the U.S population is more diverse.*

Table 38: Baseline Assessments

	Clobetasol Shampoo	Dermoval™ Gel	Vehicle Shampoo
Global Severity Score (0-5)	3.54±0.62	3.46±0.59	3.65±0.59