Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Clobetasol Propionate

Proprietary Product Name: Clobex

Sponsor: Galderma Australia Pty Ltd

18 January 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	adverse event
ANCOVA	analysis of covariance
ANOVA	analysis of variance
BP	blood pressure
BSA	body surface area
CC	Cyclocort Cream®
CPS	clobetasol propionate spray
CPSH	clobetasol propionate shampoo
DAE	discontinuation due to AE
DLQI	Dermatology Life Quality Index
HPA	hypothalamic pituitary axis
IGA	Investigator Global Severity Assessment
IOP	intraocular pressure
ITT	intention to treat
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MED	Minimal erythema dose
min	minute
NSAID	non-steroidal anti-inflammatory drug
ODS	overall disease severity
POQL-12	Koo Menter Psoriasis Index 12-Item Psoriasis Quality of Life Questionnaire
PUVA	psoralen plus ultraviolet light
SAE	serious adverse event
SD	standard deviation

Abbreviation	Meaning
SE	standard error
SOC	system organ classification
TDSS	total disease severity score
TEEC	Temovate E® emollient cream
TPS	target plaque severity
95% CI	95% confidence interval

1. Clinical rationale

The product is intended as treatments for psoriasis.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

There were four studies that provided evaluable data regarding the pharmacokinetics of clobetasol in the shampoo formulation. Study 1.CG.03.SRE.4651 provided data with regard to dermal absorption and Study RD.06.SRE.18075, Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070 provided data with regard to systemic exposure.

There were [information redacted] studies that provided pharmacodynamic data There were [information redacted] studies that used the vasoconstrictor assay: [information redacted], and Study 1.CG.03.SRE.2618 with the shampoo formulation. There were [information redacted] studies of HPA axis suppression: [information redacted] and two studies using the shampoo formulation, Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070.

There were [information redacted] "proof of concept" studies: [information redacted] and Study 1.CG.03.SRE.2577 using the shampoo formulation.

[information redacted]

There were five pivotal efficacy studies submitted in support of CPSH. There were two studies comparing CPSH with vehicle: Study RD.06.SRE.18075 and Study RD.06.SRE.18076. There was one study comparing CPSH with vehicle and with clobetasol propionate 0.05% gel: Study RD.03.SRE.2665. There were two comparator controlled studies: Study RD.03.RDE.2638 and Study RD.03.SRE.2648. There was one additional supportive study: Study 1.CG.03.SRE.2591.

There were three studies evaluable only for safety: Study GLI.04.SRE.US10029, Study GLI.04.SRE.US10085 and Study 1.CG.03.SRE.2578.

Periodic Safety Update reports were provided for clobetasol propionate that covered the time period 29 June 2005 to 28 February 2011. Summary bridging reports were provided that covered the time period 17 March 2003 to 28 February 2010.

2.2. Paediatric data

The submission did not include paediatric data. The Sponsor states: "Clobex Shampoo & Spray have not been evaluated in children or adolescents (<18 years of age) in clinical studies to date."

2.3. Good clinical practice (GCP)

Each of the study reports submitted in the application contain statements of adherence to GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

There were four studies that provided evaluable data regarding the pharmacokinetics of clobetasol in the shampoo formulation. Study 1.CG.03.SRE.4651 provided data with regard to dermal absorption and Study RD.06.SRE.18075, Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070 provided data with regard to systemic exposure.

[information redacted]

3.2. Pharmacokinetic data for clobetasol propionate shampoo

There were four studies that reported plasma concentration data for clobetasol propionate shampooy but the majority of the estimations were below the LLOQ. Hence the pharmacokinetic parameters for clobetasol in the shampoo formulation were not reported.

Study 1.CG.03.SRE.4651 was an in vitro study of the liberation-penetration of clobetasol propionate applied as two different formulations to donor skin samples. The study used six skin samples from different female donors. The study formulation was Clobex shampoo 0.05% (CPSH). There were 12 cells each treated with 10 mg of formulation (5 µg of clobetasol) per 1 cm^2 of cell. Static diffusion was allowed in the cells for 16 hours. After 15 minutes the amount of clobetasol recovered in the epidermis was ≤0.002 µg (that is, 0.06%) of the applied dose. After 16 hours the mean (SE) colbetasol recovered from the dermis was 0.81 (0.25) µg (19% of the administered dose).

Study RD.06.SRE.18075 was a multicentre, randomised, double blind, parallel group study of the efficacy and safety of CPSH 0.05% compared with vehicle in subjects with scalp psoriasis. The study included males and females 12 years of age or older with moderate to severe scalp psoriasis defined as Global Severity of at least 3 (Table 1). The active study treatment was CPSH 0.05%, applied once daily to the affected areas of the scalp, and after 15 minutes lathered and rinsed. A total of 148 subjects were randomised: 99 to CPSH, and all were included in ITT analysis. There were 82 (55.4%) females, 66 (44.6%) males, and the age range was 13 to 82 years. Plasma clobetasol concentrations were collected and analysed at Week 4 or EOS. Of 126 plasma samples that were collected and analysed only one had a clobetasol concentration above the LLOQ (<0.20 ng/mL). This concentration was 0.426 ng/mL.

Table 1. Global severity score

0	**Clear**	**Plaque thickening**=none (no elevation or thickening over normal skin) **Scaling**=none (no evidence of scaling) **Erythema**=±(hyperpigmentation or residual red colouration)
1	**Minimal**	**Plaque thickening**=±(possible but hard to ascertain if there is a slight elevation above normal skin level) **Scaling**=± (residual dryness and scaling) **Erythema**=up to mild (up to light red or pink colouration)
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 colouration)
3	**Moderate**	**Plaque thickening**=moderate (moderate elevation with rounded or sloped edges) **Scaling**=coarser (most lesions at least partially covered) **Erythema**=moderate (definite red colouration)
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**=severe (very bright red colouration)
5	**Very severe**	**Plaque thickening**=very marked (very marked elevation typically with hard sharp edges) **Scaling**=very coarse (thick tenacious scale covers most or all of the lesions) **Erythema**=very severe (extreme red colouration; deep red colouration)

Study 1.CG.03.SRE.2620 was a single centre, randomised, Investigator masked, competitor controlled, four parallel group study of opthalmological irritation potential and HPA suppression potential of CPSH in subjects with either scalp psoriasis or seborrhoeic dermatitis. The study included males and females; 18 years of age or older, with normal ocular status; normal HPA axis functioning at inclusion; scalp psoriasis or scalp seborrhoeic dermatitis; and a Total Dermatological Sum Score of at least 3. The study treatments were:

1. Clobetasol shampoo: once daily 15-minute application on dry hair for scalp psoriasis or twice a week 15-minute application on dry hair for scalp seborrhoeic dermatitis
2. Dermoval / Temovate gel, once daily application for either scalp psoriasis or seborrhoeic dermatitis.

Treatment duration was for 4 weeks.

The outcome measures were:

- Opthalmological examination by slit lamp
- IOP

- HPA axis function assessed by cosyntropin stimulation test
- Visual acuity
- Total dermatological sum score
- Routine laboratory tests
- Clobetasol plasma concentrations
- AEs

There were 52 subjects enrolled, and four subjects withdrew. There were 27 subjects treated with CPSH; 14 of whom had psoriasis. There were 25 subjects treated with Dermoval/Temovate; twelve of whom had psoriasis. There were 28 (53.8%) males, 24 (46.2%) females, and the age range was 18 to 56 years. None of the 45 samples tested for clobetasol concentrations were above the LLOQ.

Study RD.06.SRE.18070 was a multicentre, open label, study of HPA axis suppression and safety. The study included males and females, 12 to 17 years of age with moderate to severe scalp psoriasis with at least of 25% of the surface area of the scalp being involved. The study treatment was CPSH 0.05% once daily for 4 weeks and there was no reference treatment. The outcome measures were: HPA axis suppression assessed by cosyntropin stimulation test; plasma clobetasol concentrations; AEs; and laboratory safety tests. There were 13 subjects enrolled and all were included in the safety analysis. There were three (23.1%) males, ten (76.9%) females and the age range 12 to 17 years. All the plasma clobetasol concentrations were below LLOQ.

3.3. Summary of pharmacokinetics

In donor skin samples, 0.06% of the administered dose of clobetasol in the shampoo formulation was absorbed following a 15 minute exposure and 19% was absorbed during a 16 hour exposure. However, the donor skin samples were healthy skin and the absorption of clobetasol by diseased skin may be greater.

The plasma samples assayed for clobetasol in subjects treated with the shampoo formulation were, with the exception of one sample, below the LLOQ.

3.4. Evaluator's overall conclusions on pharmacokinetics

Exposure to Clobex shampoo in accordance with the instructions in the Product Information did not to lead to quantifiable systemic exposure to clobetasol propionate using the methods available to the Sponsor.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

There were [information redacted] studies that provided pharmacodynamic data. There were [information redacted] studies that used the vasoconstrictor assay: [information redacted] and Study 1.CG.03.SRE.2618 with the shampoo formulation. There were [information redacted] studies of HPA axis suppression: [information redacted]; and two studies using the shampoo formulation, Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070.

4.2. Summary of pharmacodynamic data

4.2.1. Studies of vasoconstrictor effect

Study 1.CG.03.SRE.2618 was a single centre, randomised, intra-individual, investigator blinded, active and vehicle controlled vasoconstrictor assay. The study included healthy volunteers that passed a Stoughton pre-test. The study treatments were:

a. CPSH 0.05%

b. Clobetasol 0.05% (Temovate) cream

c. Clobetasol 0.05% (Temovate) scalp application

d. Betamethasone dipropionate 0.05% (Diprolene) cream

e. Clobetasol shampoo vehicle

The test dose was 50 µL of each product under occlusive patches. The treatments were applied for 16 hours over 2 days as the pre-test dose, and as a 15 minute application over a 2 day period as the test dose. Application was topical to the forearm. Evaluation of vasoconstriction was on a 0 to 4 visual score at 4, 6, 8, 10, 12, 14 and 24 hours after removal of excess product on each treated site and on a non-treated site. The primary outcome measure was the AUC for vasoconstriction. Chromatometric measurements were used as secondary outcome measures. Sixteen healthy volunteers were enrolled for the Stoughton pre-test and 12 performed the test (all male, aged 25 to 35 years). CPSH produced significantly more vasoconstriction than vehicle or the untreated test site (Table 2). However, CPSH produced significantly less vasoconstriction than either Temovate product and similar vasoconstriction to Diprolene . There was one AE: rhinitis. There were no AEs related to test material, no SAEs, deaths or DAEs.

Table 2. Vasoconstriction results

Results of vasoconstriction evaluation	Clobetasol propionate 0.05% shampoo	Temovate® cream	Temovate® scalp application	Diprolene® cream	Clobetasol propionate shampoo vehicle	Untreated site
Activity Parameter(s):						
Visual scoring (mean ± SD of 2 evaluators)						
H4	0.31 ± 0.45	0.54 ± 0.72	1.19 ± 0.92	0.06 ± 0.11	0.04 ± 0.10	0.06 ± 0.16
H6	0.31 ± 0.40	0.81 ± 0.75	1.58 ± 0.90	0.04 ± 0.10	0.08 ± 0.22	0.13 ± 0.31
H8	0.48 ± 0.86	1.06 ± 0.92	1.96 ± 1.18	0.15 ± 0.25	0.04 ± 0.10	0.04 ± 0.10
H10	0.52 ± 0.81	1.54 ± 1.08	2.35 ± 1.22	0.17 ± 0.27	0.04 ± 0.10	0.04 ± 0.10
H12	0.50 ± 0.56	1.31 ± 0.86	2.17 ± 1.08	0.13 ± 0.23	0.0 ± 0.0	0.02 ± 0.07
H14	0.48 ± 0.57	1.21 ± 0.87	2.06 ± 1.07	0.15 ± 0.23	0.02 ± 0.07	0.02 ± 0.07
H24	0.46 ± 0.44	0.81 ± 0.56	0.94 ± 0.78	0.17 ± 0.25	0.0 ± 0.0	0.0 ± 0.0
Mean AUC values (H24)	**9.77**	**22.46****	**36.90****	**2.86***	**0.59****	**0.78****
Chromametric measurements a* parameter scores (mean difference from baseline ± SD)						
H4	0.03 ± 1.34	-0.22 ± 1.61	-0.57 ± 1.36	0.33 ± 1.14	0.43 ± 0.78	0.63 ± 1.05
H6	-0.78 ± 1.12	-1.39 ± 1.23	-1.70 ± 0.93	-0.49 ± 0.96	-0.09 ± 0.60	-0.1 ± 0.93
H8	-0.29 ± 1.61	-1.13 ± 1.61	-1.32 ± 1.24	0.17 ± 1.53	0.48 ± 0.91	0.71 ± 1.26
H10	-0.38 ± 1.3	-1.34 ± 1.39	-1.50 ± 1.35	0.29 ± 1.35	0.74 ± 0.86	0.74 ± 1.23
H12	-0.57 ± 1.18	-1.63 ± 0.95	-1.59 ± 1.19	-0.03 ± 1.02	0.45 ± 0.82	0.63 ± 1.20
H14	-0.67 ± 1.74	-1.69 ± 1.20	-1.72 ± 0.98	-0.42 ± 1.45	0.22 ± 1.06	0.38 ± 1.13
H24	-1.67 ± 0.85	-1.23 ± 0.66	-1.20 ± 0.89	-0.84 ± 1.13	-0.29 ± 0.58	-0.1 ± 0.61
Mean AUC values (H24)	**-16.28**	**-27.87***	**-30.28***	**-5.75**	**4.37****	**7.74****
L* parameter scores (mean difference from baseline ± SD)						
H4	0.72 ± 1.62	0.69 ± 2.04	2.02 ± 2.02	-0.07 ± 1.25	0.35 ± 1.57	-0.02 ± 0.81
H6	1.05 ± 1.63	1.41 ± 1.76	2.67 ± 2.12	0.40 ± 1.19	0.49 ± 1.36	0.25 ± 1.33
H8	1.30 ± 1.77	2.02 ± 1.91	3.15 ± 2.04	0.65 ± 1.21	0.64 ± 1.60	0.55 ± 1.33
H10	1.17 ± 1.38	2.24 ± 1.82	3.32 ± 1.93	0.55 ± 1.16	0.36 ± 1.40	0.26 ± 1.03
H12	1.47 ± 1.18	2.45 ± 1.70	3.26 ± 1.71	0.85 ± 0.95	0.68 ± 1.40	0.67 ± 0.86
H14	1.44 ± 1.79	2.37 ± 1.63	3.52 ± 1.85	1.12 ± 1.15	0.68 ± 1.42	0.82 ± 1.30
H24	0.36 ± 1.82	0.47 ± 2.40	1.94 ± 1.69	0.08 ± 1.42	-0.44 ± 1.99	0.04 ± 1.28
Mean AUC values (H24)	**22.64**	**34.92**	**61.97****	**11.78**	**7.32**	**8.54**

* p <0.05 versus Clobetasol propionate shampoo, 0.05%
** p <0.01 versus Clobetasol propionate shampoo, 0.05%

4.2.2. Studies of pituitary adrenal axis suppression

In Study 1.CG.03.SRE.2620, there was a non-significant decrease in cosyntropin response in the psoriasis subjects treated with CPSH daily for 4 weeks, but no individual subject was reported with adrenal suppression. The mean (SD) response at baseline was 12.03 (5.04) µ/dL and at end-point was 10.03 (3.61) µg/dL (Table 3). There was no apparent increase in IOP.

Table 3. Safety results

Safety Results (Mean ± SD) **Scalp psoriasis (PSO)**	**Clobetasol propionate shampoo 0.05%**			**Dermoval® / Temovate® gel 0.05%**		
• *HPA axis Function*	**N**	**Mean ± SD**		**N**	**Mean ± SD**	
Serum cortisol levels (μg/dl) before Cosyntropin stimulation						
Baseline	14	21.30±7.35		12	22.36±7.69	
End-point	14	23.53±10.65		12	22.24±7.44	
Increase of serum cortisol levels after Cosyntropin stimulation						
Baseline	14	12.03±5.04		12	10.89±5.59	
End-point	14	10.38±3.61		12	9.22±5.24	
• *Ocular safety*						
Intraocular pressure						
Baseline	14	13.79±1.74		12	13.92±1.78	
End-point	14	13.36±1.59		12	13.29±1.51	
Overall ocular safety	The overall ocular tolerance was excellent for both products in all the subjects. No altered signs were reported during the study.					
• *Other assessments*	**N**	**Mean ± SD**		**N**	**Mean ± SD**	
DSS						
Baseline	14	5.84±1.44		12	4.99±0.97	
End-point	14	1.76±1.55		12	1.20±0.93	
Clobetasol Plasma levels						
End-point	14	< detection limit		12	< detection limit	
Skin atrophy						
Baseline	14	1.93±0.30		12	1.71±0.24	
End-point	14	1.88±0.25		11	1.63±0.31	
Telangiectasis	**N**	**Score**	**%**	**N**	**Score**	**%**
Baseline	14	0	100	12	0	100
End-point	14	0	100	11	0	100

In Study RD.06.SRE.18070, the response to cosyntropin was, mean (SD), 17.00 (5.526) μg/dL at baseline and 15.60 (9.310) at end of study. Eight (61.5%) subjects were clear or had minimal severity after 4 weeks treatment. The mean surface area involvement decreased from 42% to 25.2%. There was one subject with HPA axis suppression, but the results of this were discarded by the Sponsor according to the following explanation (copied from page 64 of the study report):

> *"[information redacted] with skin phototype had a 3-year history of skin psoriasis and a current episode duration of 3 months. The subject had no previous or concomottant therapies. Her Baseline global severity rating was moderate. At study initiation, 35% of her scalp surface area was involved. The subject used a weekly average of 43.7 g of Clobetasol Propionate shampoo, 0.05%. Doubtful serum cortisol values were detected at Week 4 (pre-stimulation, 12.3 mcg/dL; post-stimulation 10.4 mcg/dL; change 1.9 mcg/dL). Per a memo by the central laboratory analysing cortisol levels, these pre- and post- stimulation values should be disregarded because pre- and post-specimens were not run the same day, and when subsequent testing was performed testing should have included both the pre- and post-stimulation specimens to ensure there was no mix-up between the two, Additionally, a paediatric endocrinologist evaluated the cortisol levels and concluded that they were not valid. For further information please refer to Appendix 16.1.14 for the central laboratory memorandum and the letter by the paediatric endocrinologist. HPA axis function parameters were determined to be normal by the first re-test (15 days after discontinuation of treatment). Systemic exposure as measured by plasma clobetasol were below the limit of quantification (BLQ [<0.20 ng/mL]). Routine chemistry and haematology were all with normal limits except for hemtocrit which was low at Screening and at Week 4 (39% and 37.6%, respectively). Vital signs were all within normal limits except for a change in supine blood pressure from 110/80 mm Hg at Screening to 132/104 mm Hg at the*

end of follow-up (Week 6). The subject's blood pressure findings at Week 4 were normal (119/79 mm Hg [supine] and 120/82 [standing]). At the end of follow-up (Week 6) the standing blood pressure was 142/109 mm Hg (110/76 mm Hg at Screening)."

However, in the opinion of the evaluator, these findings should have been accepted and indicate HPA suppression and treatment emergent hypertension in the subject.

4.3. Evaluator's overall conclusions on pharmacodynamics

Clobetasol propionate 0.05% in the shampoo formulation had lesser potency than the cream and scalp applications, but had similar potency to a betamethasone dipropionate 0.05% cream formulation (Study 1.CG.03.SRE.2618). The EU document "Clinical Investigation of Corticosteroids Intended for Use on the Skin", adopted February 1987, comments that the vasoconstrictor assay can be used as a preliminary rough guide to anti-inflammatory activity. However, the relationship between the vasoconstrictor assay and effectiveness in treating psoriasis is not clear.

[information redacted]

The shampoo formulation appeared to have less potential for HPA axis suppression, but one subject did have evidence of HPA axis suppression and treatment emergent hypertension (Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070).

With regard to bioequivalence, the Sponsor has justified the absence of pharmacokinetic data by arguing that the pharmacodynamic studies study the actual effects of systemic exposure, and the presentation of pharmacodynamic studies makes the presentation of pharmacokinetic data unnecessary. However, the pharmacodynamic studies were not designed in order to demonstrate bioequivalence and did not compare the responses as ratios (90% CI). [information redacted]. Clobetasol propionate 0.05% in the shampoo formulation had lesser potency than the cream and scalp applications (Study 1.CG.03.SRE.2618). Bioequivalence, as such, cannot be determined from the data.

5. Phase II studies

There were two Proof of Concept Studies: [information redacted] and Study 1.CG.03.SRE.2577 using the shampoo formulation.

5.1. Proof of concept study for clobetasol propionate shampoo

5.1.1. Study 1.CG.03.SRE.2577

Study 1.CG.03.SRE.2577 was a single centre, randomised, investigator masked, evaluation of efficacy and tolerance of a shampoo containing clobetasol propionate 0.05% after different short contact application times in scalp psoriasis. The study included subjects aged 18 to 65 years with stable scalp psoriasis (defined as a total severity score ≥2), and with a wash-out period of 3 weeks for systemic psoriasis treatments, 4 weeks for topical corticosteroids and 2 weeks for other topical scalp treatments. The study treatments were:

- clobetasol propionate 0.05% shampoo with application times of 2.5, 5 and 10 minutes;
- Dermoval foaming gel; and
- CPSH vehicle.

There was a 2 week treatment period followed by a 2 week follow-up. Subjects were assessed for desquamation, plaque thickness, erythema, itching and global improvement. The safety outcome measures were irritation symptoms (burning) and AEs. There were 60 subjects, 12 in

each group. There were 37 (31.7%) females, 23 (38.3%) males, and the age range was 19 to 63 years. The number (%) subjects with global improvement was eleven (92%) subjects for 2.5 min, nine (75%) for 5 min, nine (75%) for 10 min, twelve (100%) for Dermoval and three (25%) for vehicle. Desquamation, plaque thickness, erythema and itching improved in all of the active treatment groups.

5.2. Evaluator's overall conclusions on Phase II studies

The Phase II studies indicated potential benefit for both formulations and supported carrying the products through to Phase III. They were also useful in developing the outcome measures. However, there was limited evaluation of dosing with no evaluation of different concentrations of clobetasol propionate. There was limited evaluation of different application methods in the shampoo formulation. Some of these limitations were addressed in the Phase III studies.

6. Clinical efficacy

6.1. Efficacy data for clobetasol propionate shampoo

6.1.1. Study RD.06.SRE.18075

6.1.1.1. Study design, objectives, locations and dates

Study RD.06.SRE.18075 was a multicentre, randomised, double blind, parallel group study of the efficacy and safety of CPSH 0.05% compared with vehicle in subjects with scalp psoriasis. The study was sponsored by Galderma and conducted from 24th April 2001 to 24th July 2001 at twelve study centres in the US.

Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females 12 years of age or older
- Moderate to severe scalp psoriasis defined as Global Severity of at least 3

The exclusion criteria included:

- A history of or ongoing physical condition which in the Investigator's opinion could have put the subject at risk, confounded the study assessments, or interfered with the subject's participation in the study
- Subjects with scalp psoriasis that needed systemic treatment or those who required the use of other concomitant therapies for psoriasis during the study
- Topical corticosteroids or antipsoriatic drugs on the scalp within 2 weeks
- Topical corticosteroids on the body within 2 weeks
- Systemic corticosteroids within 4 weeks
- PUVA therapy within 6 weeks
- Systemic immunosuppressive drugs (such as azathioprine, methotrexate, tacrolimus, cyclosporine, and mycophenolate) within 8 weeks
- Systemic retinoids (such as isotretinoin, acitretin) within 16 weeks
- Other treatment that could have aggravated psoriasis (β-blockers, lithium, antimalarials and NSAIDs) within 2 weeks

- Subjects who had prolonged exposure to sunlight during the 2-week period before study entry

Study treatments

The study treatments were:

1. CPSH 0.05%
2. Vehicle

The treatments were applied once daily to the affected areas of the scalp, and after 15 minutes lathered and rinsed.

Efficacy variables and outcomes

The primary efficacy outcome measure was treatment success as measured by the Global Severity score (success rate was defined as the proportion of subjects with a Global Severity score of clear or minimal) (Table 1). The secondary efficacy outcome measures were:

- Total severity score (the sum of the individual scores for erythema, scaling and plaque thickening)
- Erythema, plaque thickening and scaling scores
- Scalp surface area of involvement
- Global assessment of improvement by the investigator and subject (Table 4).

Table 4. Global assessment of improvement (as per Investigator)

5	**Clear**	All signs and symptoms of disease have resolved (100% improvement from Baseline)
4	**Almost clear**	Nearly all signs and symptoms 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 improvement**	Significant improvement, but many signs and symptoms remain (about 50% 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 than baseline**	Worse than Baseline

The safety outcome measures were AEs and routine laboratory tests. The schedule of study visits was detailed in the study report.

Sample size

The sample size calculation used a ratio of 2:1 for allocation of subjects to CPSH and vehicle; success rates of 60% for CPSH and 20% for vehicle (from Phase I and II data); a power of 90% and level of significance of 0.05 for a 2-tailed test. This resulted in a sample size of 80 subjects in the CPSH group and 40 in the vehicle. Allowing for a 10% drop-out rate, the final sample size was determined to be 132 subjects.

Statistical methods

Hypothesis tests were tests for superiority using the Cochran-Mantel-Haenszel test adjusted for centre. Hypothesis tests were two-sided with a level of significance of 0.05.

Participant flow

A total of 148 subjects randomised: 99 to CPSH and 49 to vehicle, and all were included in ITT analysis. There were 91 (91.9%) subjects in the CPSH group and 45 (91.8%) in the vehicle that completed the study. Two (2.0%) subjects in the CPSH group and one (2.0%) in the vehicle discontinued because of an AE.

Baseline data

There were 82 (55.4%) females, 66 (44.6%) males, and the age range was 13 to 82 years. The treatment groups were similar in demographic characteristics and in skin phototype.

Results for the primary efficacy outcome

CPSH was superior to vehicle for the primary efficacy outcome variable. Success was reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, p=0.012. By Global Severity score seven (7.1%) subjects in the CPSH group and one (2.0%) in the vehicle were clear at Week 4, p = 0.005 (Table 5). However, the subgroup analysis suggests that response was greater in males than females (Table 6).

Table 5. Summary of full-scale Global Severity score at baseline and the Week 4 endpoint, ITT population

Global Severity Score (Full-Scale)	Clobetasol Propionate Shampoo, 0.05% (N=99)		Clobetasol Propionate Shampoo Vehicle (N=49)		p-value[1]
	n	(%)	n	(%)	
Baseline					
Moderate	76	(76.8)	35	(71.4)	
Severe	20	(20.2)	13	(26.5)	
Very severe	3	(3.0)	1	(2.0)	
Total	99	(100)	49	(100)	0.455
Week 4 Endpoint[2] (LOCF)					
Clear	7	(7.1)	1	(2.0)	
Minimal	21	(21.2)	4	(8.2)	
Mild	31	(31.3)	11	(22.4)	
Moderate	33	(33.3)	28	(57.1)	
Severe	7	(7.1)	4	(8.2)	
Very severe	0	(0)	1	(2.0)	
Total	99	(100)	49	(100)	0.005

[1] The p-values were based on the Cochran-Mantel-Haenszel row mean difference statistic, RIDIT transformed score, controlling for center.

[2] Endpoint = the last observation recorded for a subject during the treatment period, including Baseline if no post-baseline data were available.

ITT = intent-to-treat; LOCF = last observation carried forward; N = total number of subjects evaluable at the specific time point.

Table 6. Subgroup analysis of success rates at the Week 4 endpoint, LOCF, ITT population

		Clobetasol Propionate Shampoo, 0.05%	Clobetasol Propionate Shampoo Vehicle	p-value[1]
Gender				
Female	n/N (%)	13/53 (24.5)	4/29 (13.8)	0.255
Male	n/N (%)	15/46 (32.6)	1/20 (5.0)	0.017
Age				
12 to 17 years	n/N (%)	3/3 (100)	0/3 (0)	0.025
18 to 64 years	n/N (%)	22/80 (27.5)	4/37 (10.8)	0.044
≥65 years	n/N (%)	3/16 (18.8)	1/9 (11.1)	0.624
Race				
Caucasian	n/N (%)	23/85 (27.1)	4/45 (8.9)	0.016
Non-Caucasian	n/N (%)	5/14 (35.7)	1/4 (25.0)	0.697
Center				
[information redacted]	n/N (%)	2/14 (14.3)	0/7 (0)	0.305
	n/N (%)	2/12 (16.7)	1/6 (16.7)	1.000
	n/N (%)	6/12 (50.0)	3/6 (50.0)	1.000
	n/N (%)	2/10 (20.0)	1/5 (20.0)	1.000
	n/N (%)	4/10 (40.0)	0/4 (0)	0.149
	n/N (%)	2/9 (22.2)	0/4 (0)	0.325
	n/N (%)	2/7 (28.6)	0/4 (0)	0.260
	n/N (%)	1/6 (16.7)	0/3 (0)	0.480
	n/N (%)	1/6 (16.7)	0/3 (0)	0.480
	n/N (%)	6/13 (46.2)	0/7 (0)	0.036
Global Severity at Baseline				
Moderate	n/N (%)	25/76 (32.9)	5/35 (14.3)	0.041
Severe	n/N (%)	3/20 (15.0)	0/13 (0)	0.149
Very severe	n/N (%)	0/3 (0)	0/1 (0)	NA

[1] The p-values were based on the Cochran-Mantel-Haenszel test.
[2] Success was defined as a subject with a global severity score of 0 (clear) or 1 (minimal); n/N: n=number of successes, N=total number in subgroup.
[3] Endpoint = the last observation recorded for a subject during the treatment period, including Baseline if no post-baseline data.

Results for other efficacy outcomes

Change from baseline in total severity score was greater in the CPSH group: LS mean difference (95% CI) -1.2 (-1.8 to -0.6), p <0.001. Erythema, scaling and plaque thickening all improved in the CPSH group relative to vehicle (Table 7). Pruritus also improved in the CPSH group relative to vehicle (Table 8). The global improvement scores for both Investigator and Subjects indicated significant improvement in the CPSH group relative to vehicle (Table 9). The change from baseline in % of scalp surface area involved was greater in the CPSH group: LS mean difference (95% CI) -9.28 (-14.46 to -4.09), p <0.001.

Table 7. Severity of erythema, scaling and plaque thickening at baseline and at the Week 4 endpoint, ITT population

			Clobetasol Propionate Shampoo, 0.05% (N=99)	Clobetasol Propionate Shampoo Vehicle (N=49)	p-value[1]
Erythema Severity	***Baseline***				
	Mild	*n (%)*	3 (3.0)	1 (2.0)	0.766
	Moderate	*n (%)*	69 (69.7)	34 (69.4)	
	Severe	*n (%)*	27 (27.3)	14 (28.6)	
	Week 4 Endpoint[2]				
	None	*n (%)*	12 (12.1)	1 (2.0)	0.005
	Mild	*n (%)*	50 (50.5)	19 (38.8)	
	Moderate	*n (%)*	31 (31.3)	23 (46.9)	
	Severe	*n (%)*	6 (6.1)	6 (12.2)	
Scaling Severity	***Baseline***				
	Mild	*n (%)*	1 (1.0)	0 (0)	0.516
	Moderate	*n (%)*	59 (59.6)	32 (65.3)	
	Severe	*n (%)*	39 (39.4)	17 (34.7)	
	Week 4 Endpoint[2]				
	None	*n (%)*	15 (15.2)	2 (4.1)	0.012
	Mild	*n (%)*	43 (43.4)	15 (30.6)	
	Moderate	*n (%)*	33 (33.3)	26 (53.1)	
	Severe	*n (%)*	8 (8.1)	6 (12.2)	
Plaque Thickening Severity	***Baseline***				
	None	*n (%)*	0 (0)	2 (4.1)	0.872
	Mild	*n (%)*	22 (22.2)	6 (12.2)	
	Moderate	*n (%)*	65 (65.7)	35 (71.4)	
	Severe	*n (%)*	12 (12.1)	6 (12.2)	
	Week 4 Endpoint[2]				
	None	*n (%)*	34 (34.3)	5 (10.2)	0.006
	Mild	*n (%)*	35 (35.4)	21 (42.9)	
	Moderate	*n (%)*	27 (27.3)	21 (42.9)	
	Severe	*n (%)*	3 (3.0)	2 (4.1)	

[1] The p-values were based on the Cochran-Mantel-Haenszel row mean difference statistic, RIDIT transformed score, controlling for center.

[2] Endpoint = the last observation recorded for a subject during the treatment period, including Baseline if no post-baseline data.

ITT = intent-to-treat; N = total number of subjects (ITT) in the group; n = number of subjects with erythema, scaling, or plaque thickening.

Table 8.Severity of pruritus at baseline and the Week 4 endpoint, LOCF, ITT population

			Clobetasol Propionate Shampoo, 0.05% (N=99)	Clobetasol Propionate Shampoo Vehicle (N=49)	p-value[1]
Pruritus	***Baseline***				
	None	*n (%)*	2 (2.0)	0 (0)	0.926
	Mild	*n (%)*	17 (17.2)	9 (18.4)	
	Moderate	*n (%)*	57 (57.6)	29 (59.2)	
	Severe	*n (%)*	23 (23.2)	11 (22.4)	
	Week 4 Endpoint[2]				
	None	*n (%)*	41 (41.4)	8 (16.3)	0.001
	Mild	*n (%)*	34 (34.3)	19 (38.8)	
	Moderate	*n (%)*	17 (17.2)	14 (28.6)	
	Severe	*n (%)*	7 (7.1)	8 (16.3)	

[1] The p-values were based on the Cochran-Mantel-Haenszel row mean difference statistic, RIDIT transformed score, controlling for center.

[2] Endpoint = the last observation recorded for a subject during the treatment period; Baseline was to be carried forward if no post-Baseline data were available.

ITT = intent-to-treat; N = total number of subjects (ITT) in the group; n = number of subjects with pruritus.

Table 9. Global improvement as per the Investigator and as per the subject, ITT population

Global Improvement at Week 4 Endpoint (LOCF)[1]		Clobetasol Propionate Shampoo, 0.05%	Clobetasol Propionate Shampoo Vehicle	p-value[2]
As Per the Investigator				
N		97 (100)	47 (100)	<0.001
Clear	*n (%)*	7 (7.2)	1 (2.1)	
Almost Clear	*n (%)*	19 (19.6)	3 (6.4)	
Marked Improvement	*n (%)*	19 (19.6)	3 (6.4)	
Moderate Improvement	*n (%)*	17 (17.5)	12 (25.5)	
Minimal Improvement	*n (%)*	18 (18.6)	19 (40.4)	
No Change	*n (%)*	12 (12.4)	6 (12.8)	
Worse	*n (%)*	5 (5.2)	3 (6.4)	
As Per the Subject				
N		97	47	<0.001
Clear	*n (%)*	5 (5.2)	1 (2.1)	
Almost Clear	*n (%)*	20 (20.6)	2 (4.3)	
Marked Improvement	*n (%)*	20 (20.6)	2 (4.3)	
Moderate Improvement	*n (%)*	17 (17.5)	13 (27.7)	
Minimal Improvement	*n (%)*	20 (20.6)	16 (34.0)	
No Change	*n (%)*	13 (13.4)	8 (17.0)	
Worse	*n (%)*	2 (2.1)	5 (10.6)	

[1] Endpoint = the last observation recorded for a subject during the treatment period; Baseline was to be carried forward if no post-Baseline data were available.

[2] The p-values were based on the Cochran-Mantel-Haenszel row mean difference statistic, RIDIT transformed score, controlling for center.

ITT = intent-to-treat; N = total number of subjects evaluable for global improvement at Week 4 Endpoint (LOCF) in each group; n = number of subjects with the respective global improvement score.

6.1.2. Study RD.03.SRE.2665

6.1.2.1. Study design, objectives, locations and dates

Study RD.03.SRE.2665 was a multicentre, randomised, investigator blinded, active and vehicle controlled three parallel group, efficacy and safety study. The study was sponsored by Galderma and conducted from 20th April 2001 to 16th July 2001 at 13 centres in Europe.

Inclusion and exclusion criteria

The inclusion criteria included:

- Male and female subjects 18 years of age or older
- Moderate to severe scalp psoriasis defined as a Global Severity Score of at least 3 (on a 6-point scale)
- At least 15% of the scalp surface area affected

The exclusion criteria included:

- Pregnant or breast feeding female subjects or females planning a pregnancy during the study
- Subjects with a physical or psychiatric condition, which in the Investigator's opinion may put the subject at risk, may confound the study results, or may interfere with the subject's participation in the study
- Subjects with a washout period on the scalp for topical anti-psoriasis medications less than 2 weeks
- Subjects with a washout period for systemic anti-psoriasis medications less than 4 weeks
- Subjects with treatment that could have aggravated psoriasis, used for less than 6 months
- Subjects known to be immuno-compromised
- Subjects with less than 2 week washout after regular exposure to the sun or who planned to receive excessive exposure during the study

Study treatments

The study treatments were:

a. CPSH 0.05%, topical, on dry hair before rinsing, 15-minute application
b. Shampoo vehicle, topical, on dry hair before rinsing, 15-minute application
c. Clobetasol propionate 0.05% gel (Dermoval gel), topical, on dry hair without rinsing

The treatments were applied once daily for a 4 week period. Treatment allocation was by pre-prepared randomisation list in a 3:3:1 ratio.

Efficacy variables and outcomes

The primary efficacy outcome measures were Global Severity Score (Table 10) and Total Severity Score (the sum of erythema, desquamation and plaque thickening each scored on a 4-point scale (from 0 to 3) on each quarter of the scalp.

Table 10. Global Severity Score

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(for example, mild erythema and scaling, eventually associated with some barely detectable plauqe elevation)
Moderate	**3**	Moderate, clearly detectable signs or symptoms (for example, definite redness with obvious scaling on a plaque that often elevated above skin level)
Severe	**4**	Severe signs and symptoms detected (for example, intense redness, profuse shedding and definite plaque thickness are most often all present)
Very severe	**5**	Very severe signs or symptoms detected (for example, Maximum erythema with heavy scale production on highly elevated plaque; in some acute phases, pustules are seen)

The secondary efficacy outcome measures were:

- Erythema
- Desquamation
- Plaque thickening
- Pruritus
- Subject's Global Assessment of Improvement (5 = clear; 4 = almost clear; 3 = marked improvement; 2 = moderate improvement; 1 = minimal improvement; 0 = no change; and -1 = worse)
- Scalp Surface Area involved

Other outcome variables were: patient survey and, in some centres, photography. The safety outcome measures were: stinging/burning; pustules/folliculitis; and AEs.

Sample size

The sample size calculation used an effect size of 0.67, a power of 90% and a level of significance of 0.05. This resulted in a sample size of 50 per group, and allowing for a 15% dropout rate, 60 subjects were to be recruited to each of the active treatment groups.

Statistical methods

The study was designed to test non-inferiority of CPSH in comparison with Dermoval and superiority in comparison with vehicle. Non-inferiority was based on the 95% CI for the difference in change from baseline in Total Severity Score with the criterion for non-inferiority being the upper 95% CI being less than 1.5. The ITT analysis used LOCF. Hypothesis tests were performed using ANCOVA and the Cochran-Mantel-Haenszel test.

Participant flow

There were a total of 144 subjects enrolled in the study: 63 in the CPSH group, 61 in the Dermoval, and 20 in the vehicle. Six (4.2%) subjects did not complete the study. All subjects

were included in the ITT population. In the per-protocol population there were 57 subjects in the CPSH group, 55 in the Dermoval and 16 in the vehicle.

Baseline data

There were 76 (52.8%) females, 68 (47.2%) males, and the age range was 18 to 78 years. The treatment groups were similar in demographic and baseline characteristics.

Results for the primary efficacy outcome

Non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in treatments in change in Total Severity Score from baseline (Dermoval - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT. CPSH was superior to vehicle, $p < 0.05$. At Week 4, Global Severity Score was similar for CPSH and Dermoval, mean (SD) score 1.7 (1.3) for CPSH and 1.1 (1.0) for Dermoval.

Results for other efficacy outcomes

For erythema, plaque thickening and desquamation, Dermoval was superior to CPSH, but CPSH was superior to vehicle, $p < 0.05$ (Table 11). For pruritus, there was no significant difference between CPSH and Dermoval, but CPSH was superior to vehicle, $p < 0.05$. For Global Assessment of Improvement from baseline to Week 4, Dermoval was superior to CPSH, $p < 0.01$, but CPSH was superior to vehicle, $p < 0.05$ (Table 11). For reduction in scalp surface area involved to Week 4, Dermoval was superior to CPSH, $p < 0.05$, but CPSH was superior to vehicle, $p < 0.05$ (Table 11). The mean (SD) scalp surface area involved at Week 4 was 24.8 (22.7) % for CPSH, 17.0 (22.7) % for Dermoval and 38.8 (23.9) % for vehicle.

Table 11. Secondary efficacy outcome measures

Results	Clobetasol Shampoo	Dermoval™ gel	Vehicle
Secondary Efficacy – ITT Population			
Erythema (scale 0 to 3) (Mean ± SD)			
Baseline	1.9±0.6	1.9±0.6	2.0±0.6
Week 4	0.8±0.7	0.5±0.6	1.1±0.7
Desquamation (scale 0 to 3) (Mean ± SD)			
Baseline	1.8±0.6	1.9±0.6	1.9±0.6
Week 4	0.6±0.7	0.4±0.6	0.9±0.7
Plaque Thickening (scale 0 to 3) (Mean ± SD)			
Baseline	1.7±0.6	1.7±0.7	1.7±0.6
Week 4	0.6±0.6	0.3±0.5	0.9±0.8
Pruritus (scale 0 to 3) (Mean ± SD)			
Baseline	1.8±0.9	1.6±0.8	1.7±0.9
Week 4	0.4±0.8	0.2±0.5	1.0±1.2
Scalp Surface Area (%) (Mean ± SD)			
Baseline	51.7±20.6	50.6±20.3	59.3±21.5
Week 4	24.8±22.7	17.0±22.7	38.8±23.9
Subject's Global Assessment of Improvement: N(%)			
Marked/Almost clear/Clear	48 (76.2%)	51 (83.6%)	10 (50.0%)
Worse	0	0	2 (10.0%)

6.1.3. Study RD.06.SRE.18076

6.1.3.1. Study design, objectives, locations and dates

Study RD.06.SRE.18076 was a multicentre, randomised, vehicle controlled, double blind, parallel group efficacy and safety trial in subjects with scalp psoriasis. The study was sponsored

by Galderma and conducted from 20th April 2001 to 19th July 2001 at 13 centres in the US and Canada.

Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females, 12 years of age or older
- Moderate to severe scalp psoriasis, defined as Global Severity of at least 3 on a scale of 0 to 5

The exclusion criteria included:

- Subjects with a history of or ongoing physical condition, which in the Investigator's opinion could have put the subject at risk, confounded the study assessments, or interfered with the subject's participation in the study
- Female subjects of childbearing potential who were not practicing an acceptable form of contraception
- Subjects with scalp psoriasis that needed systemic treatment or those who required the use of other concomitant therapies for psoriasis during the study
- Use of topical corticosteroids within 2 weeks
- Use of topical anti-psoriatic drugs on the scalp within 2 weeks
- Use of systemic corticosteroids within 4 weeks
- Use of PUVA within 6 weeks
- Use of systemic immunosuppressive drugs (azathioprine, methotrexate, tacrolimus, cyclosporine and mycophenolate) within 8 weeks
- Use of systemic retinoids (e.g. isotretinoin, acitretin) within 16 weeks
- Other treatment that could have aggravated psoriasis (β-blockers, lithium, antimalarials or NSAIDs) within 2 weeks
- Subjects who were known to be immunocompromised
- Subjects who had prolonged exposure to sunlight during the 2 week period before study entry

Study treatments

The study treatments were:

a. CPSH 0.05%

b. Vehicle

The treatments were applied once daily to dry scalp, and after waiting for 15 minutes were lathered and rinsed. Treatment duration was for 4 weeks, with a follow-up visit 2 weeks after treatment ceased.

Efficacy variables and outcomes

The primary efficacy outcome measure was the success rate at Week 4 with success defined as a Global Severity Score of clear or minimal. The secondary efficacy outcome measures were:

- Global Severity Score
- Total Severity Score
- Erythema

- Plaque thickening
- Scaling
- Pruritus
- Percentage scalp surface area of involvement
- Global assessment of improvement by the Investigator
- Global assessment of Improvement by the subject

The safety outcome measures were: AEs, skin atrophy, telangiectasis, burning, irritation and acne.

Sample size

The sample size calculation used a ratio of 2:1 for CPSH: vehicle, assumed a success rate of 60% or CPSH and 20% for vehicle, a power of 90% and a two tailed level of significance of 0.05. This resulted in 80 subjects in the CPSH group and 40 in the vehicle, and allowing for a 10% dropout rate resulted in a final sample size calculation of 132 subjects.

Statistical methods

Hypothesis tests were performed using the Cochrane-Mantel-Haenszel test stratified by centre and ANOVA.

Participant flow

There were 142 subjects randomised: 95 to CPSH and 47 to vehicle. Of these, 88 (92.6%) subjects in the CPSH group and 44 (93.6%) in the vehicle completed the study.

Baseline data

There were 82 (57.7%) females, 60 (42.3%) males, and the age range was 13 to 81 years. The treatment groups were similar in demographic characteristics and skin phenotype.

Results for the primary efficacy outcome

CPSH was superior to vehicle by the analysis of primary efficacy outcome measure. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success (Table 12). At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success. There was no apparent significant effect of subgroup on success rate (Table 13).

Table 12. Summary of success rate, ITT population

Success Rate[1] Time Point	Clobetasol Propionate Shampoo, 0.05% (N=95)			Clobetasol Propionate Shampoo Vehicle (N=47)			p-value[2]
	N	n	(%)	N	n	(%)	
Baseline	95	0	(0)	47	0	(0)	
Week 2	93	17	(18.3)	46	3	(6.5)	0.081
Week 4	91	40	(44.0)	45	1	(2.2)	<0.001
Week 4 Endpoint[3] (LOCF)	**95**	**40**	**(42.1)**	**47**	**1**	**(2.1)**	**<0.001**
Week 6 (follow-up)	88	21	(23.9)	44	2	(4.5)	0.003

[1] Success was defined as a subject with a global severity score of 0 (clear) or 1 (minimal).
[2] The p-values were based on the Cochran-Mantel-Haenszel test, controlling for center.
[3] Endpoint = the last observation recorded for a subject during the treatment period, including Baseline if there were no post-baseline data available.

ITT = intent-to-treat; LOCF = last observation carried forward; N = total number of subjects evaluable at the specific time point; n = number of subjects with success.

Table 13. Subgroup analysis of success rates at the Week 4 endpoint, LOCF, ITT population

		Clobetasol Propionate Shampoo, 0.05%	Clobetasol Propionate Shampoo Vehicle	p-value[1]
Gender				
Female	n/N (%)	23/57 (40.4)	1/25 (4.0)	<0.001
Male	n/N (%)	17/38 (44.7)	0/22 (0)	<0.001
Age				
12 to 17 years	n/N (%)	1/2 (50.0)	0/2 (0)	0.317
18 to 64 years	n/N (%)	32/80 (40.0)	1/39 (2.6)	<0.001
≥65 years	n/N (%)	7/13 (53.8)	0/6 (0)	0.028
Race				
Caucasian	n/N (%)	36/88 (40.9)	1/43 (2.3)	<0.001
Non-Caucasian	n/N (%)	4/7 (57.1)	0/4 (0)	0.071
Center				
[information redacted]	n/N (%)	4/12 (33.3)	0/6 (0)	0.119
	n/N (%)	6/10 (60.0)	0/5 (0)	0.031
	n/N (%)	3/10 (30.0)	0/5 (0)	0.186
	n/N (%)	5/9 (55.6)	1/5 (20.0)	0.215
	n/N (%)	2/9 (22.2)	0/4 (0)	0.325
	n/N (%)	2/7 (28.6)	0/3 (0)	0.326
	n/N (%)	2/6 (33.3)	0/3 (0)	0.285
	n/N (%)	3/6 (50.0)	0/3 (0)	0.157
	n/N (%)	3/6 (50.0)	0/3 (0)	0.157
	n/N (%)	2/5 (40.0)	0/3 (0)	0.237
	n/N (%)	1/4 (25.0)	0/3 (0)	0.386
	n/N (%)	7/11 (63.6)	0/4 (0)	0.035
Global Severity at Baseline				
Moderate	n/N (%)	36/70 (51.4)	1/32 (3.1)	<0.001
Severe	n/N (%)	4/20 (20.0)	0/10 (0)	0.135
Very severe	n/N (%)	0/0 (0)	0/0 (0)	NA

[1] The p-values were based on the Cochran-Mantel-Haenszel test.
[2] Success was defined as a subject with a global severity score of 0 (clear) or 1 (minimal).
[3] Endpoint = the last observation recorded for a subject during the treatment period, including Baseline if there were no post-baseline data available.

Results for other efficacy outcomes

On the Global Severity Scale the pattern of severity was less in the CPSH group, p <0.001. Total Severity Score decreased from baseline to Week 4 to a greater extent in the CPSH group: LS mean (SE) -3.2 (0.20) for CPSH and -1.1 (0.28) for vehicle, p <0.001. Erythema, scaling and plaque thickening all improved to a greater extent in the CPSH group, p <0.001. Pruritus improved to a greater extent in the CPSH group, p <0.001. Both the Investigator and the subject Global Improvement scores were better in the CPSH group, p <0.001. From baseline to Week 4 there was a decrease in % surface area involved by LS mean (SE) 17.1 (1.75) % in the CPSH group and 1.0 (2.42%) in the vehicle, p <0.001.

6.1.4. Study RD.03.RDE.2638

6.1.4.1. Study design, objectives, locations and dates

Study RD.03.RDE.2638 was a multicentre, randomised, investigator blinded, parallel group, comparator controlled study. The study was sponsored by Galderma and conducted from 26th April 2000 to 14th December 2000 at 14 studies in Europe.

Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females, 12 years of age or older

- Stable moderate to severe scalp psoriasis (defined as Global Severity of a t least 3 on a 0 to 5 point scale)
- At least 2 cm^2 of the scalp involved

The exclusion criteria included:

- Pregnant or breast feeding female subjects or female planning a pregnancy during the study
- Physical or psychiatric condition, which in the Investigator's opinion could put the subjects at risk, could confound the study results, or could interfere with the subject's participation in the study
- Subjects with very severe scalp psoriasis that needed systemic treatment or those requiring the use of other concomitant therapies for psoriasis during the study
- Topical corticosteroids or anti-psoriatic drugs within 2 weeks
- Systemic corticosteroids, immunosuppressive drugs, retinoids or treatment of calcium homeostasis within 4 weeks
- Treatment that could aggravate psoriasis (β-blockers, lithium, antimalarials, NSAIDs) within 2 weeks
- Less than a 2 week washout after regular exposure to the sun or subjects who planned to receive exposure during the study

Study treatments

The study treatments were:

a. CPSH 0.05%, once daily
b. Calcipotriol solution 0.005%, (Dovonex/ Daivonex), twice daily

Treatment duration was for 4 weeks. Treatment allocation was according to a pre-prepared randomisation list. Subjects were not blinded to treatment allocation but Investigators were.

Efficacy variables and outcomes

The primary efficacy outcome measures were Total Severity Score and Global Severity Score. The secondary efficacy outcome measures were:

- Erythema
- Plaque thickening
- Desquamation
- Puritis
- Scalp surface area involved
- Global assessment of improvement (Investigator's and subject's)

The safety outcome measures were: local safety (telangiectasis, skin atrophy, burning); ocular safety (burning/stinging); AEs; and BP.

Sample size

The sample size calculation was based on the test of non-inferiority and used historical data to predict effect size. The effect size of CPSH was estimated to be 75% and that for calcipotriol to be 50%. The SD for the reduction in Total Severity Score was estimated to be 30%. Power was taken to be 90% and the level of significance was 0.05. Assuming a dropout rate of 15%, 120 subjects (60 in each treatment group) would be required.

Statistical methods

The study was designed as a non-inferiority study based on the per protocol analysis with support from the ITT analysis. If non-inferiority were demonstrated then a secondary test of superiority was to be performed on the ITT population. Hypothesis tests were performed using ANOVA and the Cochran Mantel Haenszel test. The criterion of non-inferiority was that the upper limit of the 95% CI for the difference in Day 28 Total Severity score (CPSH - calcipotriol) should be less than 1.5 (representing a 20% difference on the scale).

Participant flow

There were 151 subjects included in the study: 76 in the CPSH group and 75 in the calcipotriol. Of these subjects, 73 in the CPSH group and 64 in the calcipitriol completed the study. In the per-protocol population there were 67 (88.2%) subjects in the CPSH group and 61 (81.3%) in the calcipitriol.

Baseline data

There were 71 (47.0%) males, 80 (53.0%), females, and the age range was 10 to 89 years. The treatment groups were similar in demographic characteristics and in baseline characteristics.

Results for the primary efficacy outcome

Non-inferiority was demonstrated on the per-protocol analysis of Total Severity Score, and superiority was demonstrated on the secondary analysis of the ITT population. The 95% CI for the difference in Day 28 Total Severity score (CPSH – calcipitriol) was -0.66 to 0.18 for the per-protocol analysis and -0.97 to -0.05 for the ITT analysis (Table 14). Superiority was also demonstrated for Global Severity score by the ITT analysis: 95% CI -0.78 to -0.08 (Table 14). Subgroup analyses were not presented.

Table 14. Primary efficacy outcome measures

Results	Clobetasol (N=76)	Calcipotriol (N=75)
TSS (Mean ±SD), PP population		
Baseline	4.82 ±1.97	4.99 ±1.53
D28	1.64 ±1.49	1.94 ±1.35
95% CI (Clobetasol - Calcipotriol) at D28	[-0.66; 0.18] < pre-specified non inferiority margin = 1.5	
TSS (Mean ±SD), ITT (LOCF) population		
Baseline	4.86 ±1.95	4.95 ±1.49
D28	1.76 ±1.57	2.36* ±1.64
95% CI (Clobetasol - Calcipotriol) at D28	[-0.97; -0.05] < pre-specified non inferiority margin = 1.5	
* p<0.05 for the superiority in TSS of clobetasol versus calcipotriol at D28		
(scale: 0-5)		
GSS (Mean ±SD), PP population		
Baseline	3.42 ±0.55	3.51 ±0.62
D28	1.42 ±1.09	1.74 ±1.17
95% CI (Clobetasol - Calcipotriol)	[-0.59; 0.06]	
GSS (Mean ±SD), ITT (LOCF) population		
Baseline	3.49 ±0.60	3.51 ±0.60
D28	1.55 ±1.20	2.03* ±1.31
95% CI (Clobetasol - Calcipotriol)	[-0.78; -0.08]	
* p<0.05 for the superiority in GSS of clobetasol versus calcipotriol at D28		
Rate of subjects with none, very mild or mild global severity at D28, ITT (LOCF) population (%).	61	47

Results for other efficacy outcomes

Although the scores for erythema, plaque thickening, adherent desquamation and pruritus appeared to be more favourable at Week 4 in the CPSH group, hypothesis tests were not presented for these variables. The scalp surface area involved decreased to a greater extent in the CPSH group: treatment difference (95% CI) (CPSH – calcipotriol) at Week 4 was: -7.33 (-13.58 to -1.09) %. Both the Investigator's and Subject's global assessment of improvement were better in the CPSH group, $p < 0.01$.

6.1.5. Study RD.03.SRE.2648

6.1.5.1. Study design, objectives, locations and dates

Study RD.03.SRE.2648 (Shampoo Module 5, Section 5.3.5.1) was a multicentre, randomised, Investigator blinded, comparator controlled, parallel group study. The study was sponsored by Galderma, and conducted from January 2001 to June 2001 at 21 centres in the UK.

Inclusion and exclusion criteria

The inclusion criteria included:

- Males and females, 18 years of age or older
- Moderate to severe scalp psoriasis (Global Severity score of at least 3 on a scale from 0 to 5)
- At least 15% of the scalp area involved

The exclusion criteria were similar to those for Study RD.03.RDE.2638 but also included: subjects who were bald.

Study treatments

The study treatments were:

a. CPSH 0.05%, once daily application, topical on dry hair for 15 minutes before rinsing
b. Polytar Liquid , twice per week application, topical on wet hair before rinsing

Subjects were randomised to treatment in a ratio of 3:1. Subjects were aware of treatment allocation but Investigators were blinded.

Efficacy variables and outcomes

The primary efficacy outcome measures were Total Severity score and Global Severity score. The secondary efficacy outcome measures were:

- Erythema
- Loose and adherent desquamation
- Plaque thickening
- Pruritus
- Patient's Global Improvement score

The safety outcome measures were: symptoms of irritation, ocular examination and AEs.

Sample size

The sample size calculation used a ratio of 3:1, CPSH to Polytar , a power of 90%, a level of significance of 0.05, a non-inferiority criterion of a difference between treatments of 1.5 points, and an effect size of 0.67 on the Total Severity score. Allowing for a 15% dropout rate, 120 subjects in the CPSH group and 40 in the Polytar would be required.

Statistical methods

The study was designed as a test of non-inferiority with a secondary test of efficacy. Total Severity score from the per-protocol population was used as the primary efficacy outcome measure and the margin for non-inferiority was 1.5 points. Hypothesis tests were performed using 95% CI from ANCOVA models, with baseline as a covariate and centre and treatment as factors. The Cochran-Mantel-Haenszel test was also used for some hypothesis tests.

Participant flow

There were 162 subjects randomised to treatment: 121 to CPSH and 41 to Polytar. Of these, 112 (93%) subjects in the CPSH and 36 (88%) subjects in the Polytar completed the study. The per-protocol analysis included 105 (86.8%) subjects in the CPSH group and 32 (78.0%) in the Polytar.

Baseline data

There were 86 (53.1%) males, 76 (46.9%) females, and the age range was 19 to 96 years. There was a higher proportion of females in the CPSH group: 51.2% compared with 34.1% in the Polytar. Baseline efficacy and safety measures were similar for the two treatment groups.

Results for the primary efficacy outcome

Non-inferiority was demonstrated in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar-CPSH) was -2.066 (-2.727 to -1.405), and the upper 95% CI was below the non-inferiority target of 1.5. Superiority was demonstrated by the secondary analysis of Total Severity score in the ITT population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar - CPSH) was -1.842 (-2.475 to -1.208), p = 0.0001. This was confirmed by the analysis of Global Severity score: mean (SD) at Week 4: 1.9 (1.0) for CPSH and 3.0 (1.0) for Polytar, p = 0.0001. A subgroup analysis was not performed.

Results for other efficacy outcomes

At Week 4 there was less erythema in the CPSH group (mean [SD] 1.2 [0.8] compared with 1.7 [0.7], p = 0.0001); less plaque thickening (0.9 [0.8] compared with 1.6 [0.9], p = 0.0001); less desquamation (1.1 [0.8] compared with 1.9 [0.8], p = 0.0001); and less pruritus (0.6 [0.8] compared with 1.2 [0.8], p <0.001). Mean (SD) scalp surface area involved was significantly less at Week 4 in the CPSH group: 28.7 (25.4) % compared with 45.6 (27.8) %, p <0.001. At Week 4, by the Subject's Global Assessment, in the CPSH group 40 (33.6%) subjects were clear or almost clear compared with three (7.7%) in the Polytar, p=0.001.

6.2. Other efficacy studies for Clobetasol Propionate Shampoo

6.2.1. Study 1.CG.03.SRE.2591

Study 1.CG.03.SRE.2591 was a multicentre, randomised, Investigator masked, comparator controlled, four parallel group study comparing application methods for CPSH in subjects with scalp psoriasis. The study was sponsored by Galderma and conducted at 13 study centres in France. The study included subjects aged 18 to 70 years, with stable scalp psoriasis (defined as presence of erythema and adherent desquamation, and plaque thickening, each scored at least 1) and at least 4 cm^2 of the scalp should be involved. The study treatments were:

a. CPSH 0.05%, 15 minute application on dry hair, once daily
b. CPSH 0.05%, 10 minute application on dry hair, once daily
c. CPSH 0.05%, 10 minute application on wet hair, once daily
d. Daivonex scalp solution, twice daily

There was a 3 week treatment phase, and a 3 week follow-up phase. The primary efficacy outcome measure was Total Severity Score and the secondary efficacy outcome measures were: erythema; loose and adherent desquamation; plaque thickening; itching; Global Improvement and patient's evaluation of cosmetic acceptance. The safety outcome measures were: symptoms of irritation; and AEs.

There were 59 subjects included in the trial and all were included in the ITT population: 15 in the CPSH 15 min dry group, 14 in the 10 min dry, 15 in the 10 min wet and 15 in the Daivonex. There were 34 (57.6%) males, 25 (42.4%) females and the age range was 18 to 69 years. For Total Severity Score the 15 min dry application was significantly better then Daivonex ($p \leq 0.05$) but this was less convincing for the other application methods. The mean (SD) Total Severity Score at endpoint was 2.1 (2.0) for 15 min dry, 2.8 (2.4) for 10 min dry, 2.1 (1.8) for 10 min wet and 3.7 (2.0) for Daivonex. The secondary efficacy outcome measures supported this finding.

6.3. Analyses performed across trials (pooled analyses and meta-analyses)

Report RD.03.DEU.0114.R00 was a post-hoc analysis of data from Studies 2638, 2648, 2665, 18075 and 18076. The report presented individual tabulations of data and limited analysis of pooled data (Studies 18075 and 18076 only). The data were from the primary efficacy endpoints. The analysis did not contribute any additional information with regards to efficacy.

6.4. Evaluator's conclusions on clinical efficacy for Clobex shampoo

CPSH was superior to vehicle in the treatment of scalp psoriasis. In Study RD.06.SRE.18075, CPSH was superior to vehicle for the primary efficacy outcome variable, Global Severity score, with success reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, $p = 0.012$. In Study RD.03.SRE.2665, CPSH was superior to vehicle by the Total Severity score, $p < 0.05$. In Study RD.06.SRE.18076, CPSH was superior to vehicle by the analysis of primary efficacy outcome measure, Global Severity Score. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success. At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success.

CPSH was non-inferior to clobetasol propionate 0.05% gel for the treatment of scalp psoriasis. In Study RD.03.SRE.2665, non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in treatments in change in Total Severity Score from baseline (Dermoval - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT. However, for some of the secondary efficacy outcome measures, clobetasol propionate 0.05% gel was superior to CPSH (Study RD.03.SRE.2665).

CPSH was superior to Calcipotriol solution 0.005%, (Dovonex/Daivonex), twice daily, and to Polytar . In Study RD.03.RDE.2638, non-inferiority was demonstrated on the per-protocol analysis of Total Severity Score, and superiority was demonstrated on the secondary analysis of the ITT population. The 95% CI for the difference in Day 28 Total Severity score (CPSH – calcipitriol) was -0.66 to 0.18 for the per-protocol analysis and -0.97 to -0.05 for the ITT analysis. In Study RD.03.SRE.2648, non-inferiority was demonstrated in comparison to Polytar in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar - CPSH) was -2.066 (-2.727 to -1.405), and the upper 95% CI was below the non-inferiority target of 1.5. Superiority was demonstrated by the secondary analysis of Total Severity score in the ITT population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar - CPSH) was -1.842 (-2.475 to -1.208), $p = 0.0001$.

In addition, Study 1.CG.03.SRE.2591 supported the administration method of 15 minute application to dry hair followed by lathering and rinsing.

The studies were conducted with robust and clinically relevant endpoints. The severity scores used the same components as the Psoriasis Area and Severity Index (PASI) and the Psoriasis Global Assessment (PGA). This included erythema, scaling and plaque elevation; and the % surface area affected. This is consistent with the "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis". In addition, the studies also evaluated pruritus. The criteria used for treatment success in Study RD.06.SRE.18076 were clinically relevant. The non-inferiority criteria were clinically significant.

6.5. Evaluator's general comments on the clinical efficacy data

There were few data on the duration of response in the submission. The treatment duration was for 4 weeks at most, and this reflects the treatment advice in the Product Information document. However efficacy assessments beyond 2 weeks after treatment cessation were not performed. This is not consistent with the "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis" which advises assessment up to 2 months after treatment cessation. Hence there are limited data in the submission on the duration of treatment effect or the risks of disease rebound/relapse. There were also no evaluable data for treatment in combination with other psoriasis treatments.

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- AEs, SAEs and DAEs
- AEs of particular interest, including application site effects such as stinging and burning
- Laboratory tests (most of the pivotal efficacy studies did not perform routine laboratory tests)

7.1.2. Dose-response and non-pivotal efficacy studies

[information redacted]

7.1.3. Other studies evaluable for safety only

[information redacted]

Study 1.CG.03.SRE.2578 was a multicentre, randomised, Investigator masked, comparator and vehicle controlled, five parallel group study of application regimens for CPSH in subjects with seborrhoeic dermatitis. The study was sponsored by Galderma, and conducted from 17th March 1998 to 2nd June 1998 at five centres in France. The study included subjects aged 18 to 70 years with scalp seborrhoeic dermatitis with a Total Severity score ≥2, and presence of erythema and desquamation, each at least 0.5. The study treatments were:

a. CPSH 0.05%, 10 minute application twice weekly, 5 or 10 mL depending on hair length
b. CPSH 0.05%, 5 minute application, twice weekly, 5 or 10 mL depending on hair length
c. CPSH 0.05%, 2.5 minute application, twice weekly, 5 or 10 mL depending on hair length

d. Shampoo vehicle, 10 minute application, twice weekly, 5 or 10 mL depending on hair length

e. Ketoderm (ketoconazole 2%) 6 g sachet, 5 minute application, twice weekly

The outcome measures were: severity score of desquamation and erythema on each quarter of the scalp; itching; AEs and patient questionnaire. Hypothesis tests were performed using the Mann-Whitney test. The study included 55 subjects, eleven in each treatment group. All the subjects were included in the ITT population. There were 30 (54.5%) males, 25 (45.5%) females, and the age range was 18 to 64 years. The best efficacy outcomes were seen in the CPSH 5 min application group.

7.1.4. Pivotal studies that assessed safety as a primary outcome

There were no additional Pivotal studies that assessed safety as a primary outcome.

7.2. Patient exposure

[information redacted]

A total of 607 subjects were exposed to CPSH for up to 4 weeks.

In Study 1.CG.03.SRE.2577, 36 subjects were treated with CPSH for 2 weeks.

In Study RD.06.SRE.18075, a total of 99 subjects were exposed to CPSH for up to 4 weeks.

In Study 1.CG.03.SRE.2620 subjects treated with CPSH for up to 4 weeks; 14 with daily applications, and 13 with twice weekly applications.

In Study RD.06.SRE.18070, there were 13 subjects exposed to CPSH 0.05% once daily for up to 4 weeks.

In Study RD.03.SRE.2665, there were 63 subjects exposed to CPSH for up to 28 days, with a mean (SD) duration of treatment of 27.26 (2.16) days.

In Study RD.06.SRE.18076, there were 95 subjects exposed to CPSH for up to 4 weeks.

In Study 1.CG.03.SRE.2591, a total of 44 subjects were exposed to CPSH 0.05% once daily for 3 weeks.

In Study RD.03.RDE.2638, there were 76 subjects exposed to daily applications of CPSH for up to 4 weeks.

In Study RD.03.SRE.2648, there were 121 subjects treated with CPSH 0.05%, once daily application, for up to 4 weeks.

In Study 1.CG.03.SRE.2578, there were 33 subjects with scalp seborrhoeic dermatitis that were exposed to CPSH twice weekly for 4 weeks.

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

7.3.1.1. Pivotal studies

[information redacted]

In Study RD.06.SRE.18075 there were 37 (37.8%) subjects in the CPSH and 18 (37.5%) in the vehicle that reported AEs. The pattern of AEs was similar for the two treatment groups (Table 15).

Table 15. Summary of AEs by body system and COSTART term.

Body System/Costart Term*	Clobetasol Shampoo (N=98)	Vehicle Shampoo (N=48)
Total Number of AE(s)	49	40
Total Number of Subjects with AE(s)^	37 (37.8%)	18 (37.5%)
RESPIRATORY SYSTEM	9 (9.2%)	5 (10.4%)
PHARYNGITIS	6 (6.1%)	3 (6.3%)
BRONCHITIS	2 (2.0%)	2 (4.2%)
ASTHMA	1 (1.0%)	0 (0.0%)
SINUSITIS	0 (0.0%)	1 (2.1%)
BODY AS A WHOLE	8 (8.2%)	7 (14.6%)
INJURY ACCID	4 (4.1%)	3 (6.3%)
PAIN	2 (2.0%)	1 (2.1%)
FLU SYND	1 (1.0%)	2 (4.2%)
SURGICAL/MED/PROC	1 (1.0%)	0 (0.0%)
HEADACHE	1 (1.0%)	0 (0.0%)
LAB TEST ABNORM	0 (0.0%)	1 (2.1%)
FEVER	0 (0.0%)	1 (2.1%)
INFECT	0 (0.0%)	1 (2.1%)
SKIN AND APPENDAGES	7 (7.1%)	10 (20.8%)
DISCOMFORT SKIN	4 (4.1%)	4 (8.3%)
URTICARIA	1 (1.0%)	0 (0.0%)
PRURITUS	1 (1.0%)	5 (10.4%)
NEOPL SKIN	1 (1.0%)	0 (0.0%)
EDEMA SKIN	1 (1.0%)	0 (0.0%)
PSORIASIS	1 (1.0%)	0 (0.0%)
DERMATITIS	0 (0.0%)	1 (2.1%)
DERM CONTACT	0 (0.0%)	1 (2.1%)
DESQUAMATION	0 (0.0%)	1 (2.1%)
IRRITANT DERMATITIS	0 (0.0%)	1 (2.1%)
ERYTHEMA	0 (0.0%)	1 (2.1%)
UROGENITAL SYSTEM	7 (7.1%)	1 (2.1%)
HEMATURIA	4 (4.1%)	0 (0.0%)
INFECT URIN TRACT	1 (1.0%)	1 (2.1%)
GLYCOSURIA	1 (1.0%)	0 (0.0%)
URIN TRACT DIS	1 (1.0%)	0 (0.0%)
DIGESTIVE SYSTEM	4 (4.1%)	4 (8.3%)
TOOTH DIS	4 (4.1%)	0 (0.0%)
CHOLELITH	1 (1.0%)	0 (0.0%)
DIARRHEA	0 (0.0%)	1 (2.1%)
NAUSEA	0 (0.0%)	2 (4.2%)
CONSTIP	0 (0.0%)	1 (2.1%)
MUSCULOSKELETAL SYSTEM	3 (3.1%)	1 (2.1%)
MYALGIA	1 (1.0%)	0 (0.0%)
ARTHRITIS	1 (1.0%)	1 (2.1%)
ARTHRALGIA	1 (1.0%)	0 (0.0%)
HEMIC AND LYMPHATIC SYSTEM	2 (2.0%)	0 (0.0%)
THROMBOCYTOPENIA	1 (1.0%)	0 (0.0%)
WBC ABNORM	1 (1.0%)	0 (0.0%)
METABOLIC AND NUTRITIONAL DISORDER	2 (2.0%)	1 (2.1%)
HYPERGLYCEM	1 (1.0%)	0 (0.0%)
EDEMA PERIPH	1 (1.0%)	0 (0.0%)
SGPT INC	0 (0.0%)	1 (2.1%)
SGOT INC	0 (0.0%)	1 (2.1%)
CARDIOVASCULAR SYSTEM	1 (1.0%)	0 (0.0%)
HYPERTENS	1 (1.0%)	0 (0.0%)
NERVOUS SYSTEM	1 (1.0%)	1 (2.1%)
DIZZINESS	1 (1.0%)	1 (2.1%)
SPECIAL SENSES	1 (1.0%)	1 (2.1%)
OTITIS EXT	1 (1.0%)	0 (0.0%)
OTITIS MED	0 (0.0%)	1 (2.1%)

In Study RD.03.SRE.2665 there were a total of four AEs reported in four (6.3%) subjects in the CPSH group (headache, diarrhoea, acne and alopecia), three in two (3.3%) subjects in the Dermoval group (headache, acne and erythema), and two in two (10.0%) subjects in the vehicle (facial oedema and pruritus). There were two treatment related AEs were reported in two (3.2%) subjects in the CPSH group (alopecia and acne), one in one (1.6%) subject in the Dermoval group (acne) and two in two (10.0%) subjects in the vehicle (facial oedema and

pruritus). There were more subjects in the CPSH group with folliculitis than in the Dermoval: four (6.5%) compared with one (1.7%) respectively (Table 16).

Table 16. Results for safety outcome measures

Results		Clobetasol Shampoo	Dermoval™ gel	Vehicle
Safety				
Cutaneous Safety: Worst Score across post-baseline visits - N (%)				
Stinging/burning:	None	54 (87.1%)	55 (91.7%)	14 (70.0%)
	Mild	7 (11.3%)	4 (6.7%)	2 (10.0%)
	Moderate	1 (1.6%)	1 (1.7%)	4 (20.0%)
Pustules/Folliculitis:	None	58 (93.5%)	59 (98.3%)	20 (100%)
	Mild	4 (6.5%)	0	0
	Moderate	0	1 (1.7%)	0

In Study RD.06.SRE.18076, AEs were reported in 36 (38.3%) subjects in the CPSH group and 16 (34.0%) in the vehicle. Overall the proportion of subjects with AEs was similar for the two treatment groups (Table 17). AEs related to study drug were reported in 13 (13.8%) subjects in the CPSH group and 10 (21.3%) in the vehicle. The most common treatment related AE was skin discomfort (Table 18).

Table 17.Summary of AEs by COSTART term

COSTART Term*	Clobetasol Shampoo (N=94)	Vehicle Shampoo (N=47)
Total Number of AE(s)	45	19
Total Number of Subjects with AE(s)^	36 (38.3%)	16 (34.0%)
DISCOMFORT SKIN	10 (10.6%)	8 (17.0%)
GASTROENTERITIS	3 (3.2%)	0 (0.0%)
INJURY ACCID	3 (3.2%)	0 (0.0%)
FLU SYND	2 (2.1%)	1 (2.1%)
HEADACHE	2 (2.1%)	0 (0.0%)
SKIN DRY	2 (2.1%)	2 (4.3%)
URTICARIA	2 (2.1%)	0 (0.0%)
ASTHENIA	1 (1.1%)	1 (2.1%)
ASTHMA	1 (1.1%)	0 (0.0%)
COLITIS	1 (1.1%)	0 (0.0%)
CONJUNCTIVITIS	1 (1.1%)	0 (0.0%)
COUGH INC	1 (1.1%)	0 (0.0%)
DYSPEPSIA	1 (1.1%)	0 (0.0%)
ECCHYMOSIS	1 (1.1%)	0 (0.0%)
ECZEMA	1 (1.1%)	0 (0.0%)
HERPES ZOSTER	1 (1.1%)	0 (0.0%)
HYPERLIPEM	1 (1.1%)	0 (0.0%)
INFECT	1 (1.1%)	0 (0.0%)
IRRITANT DERMATITIS	1 (1.1%)	1 (2.1%)
PAIN	1 (1.1%)	0 (0.0%)
PHARYNGITIS	1 (1.1%)	1 (2.1%)
PRURITUS	1 (1.1%)	3 (6.4%)
RHINITIS	1 (1.1%)	0 (0.0%)
SINUSITIS	1 (1.1%)	0 (0.0%)
SURGICAL/MED/PROC	1 (1.1%)	0 (0.0%)
TOOTH DIS	1 (1.1%)	0 (0.0%)
PSORIASIS	0 (0.0%)	2 (4.3%)

Table 18. Summary of AEs related to study drug

Body System/Costart Term*	Clobetasol Shampoo (N=94)	Vehicle Shampoo (N=47)
Total Number of AE(s)	14	13
Total Number of Subjects with AE(s)^	13 (13.8%)	10 (21.3%)
SKIN AND APPENDAGES	12 (12.8%)	10 (21.3%)
DISCOMFORT SKIN	10 (10.6%)	8 (17.0%)
PRURITUS	1 (1.1%)	3 (6.4%)
IRRITANT DERMATITIS	1 (1.1%)	1 (2.1%)
SKIN DRY	1 (1.1%)	1 (2.1%)
SPECIAL SENSES	1 (1.1%)	0 (0.0%)
CONJUNCTIVITIS	1 (1.1%)	0 (0.0%)

In Study RD.03.RDE.2638 a total of eight AEs were reported in eight (10.5%) subjects in the CPSH group and 33 in 23 (30.7%) in the calcipotriol. Four of the AEs in the CPSH group were dermatological (Table 19). In Study RD.03.RDE.2638 there was one AE in the CPSH group related to study drug (folliculitis), and 23 in the calcipotriol. Telangiectasis and burning decreased in both treatment groups (Table 20).

Table 19. AEs by body system and COSTART term

BODY SYSTEM / COSTART	Group								
	Clobetasol (N=76)			Calcipotriol (N=75)			Total (N=151)		
	#	N	%	#	N	%	#	N	%
BODY									
FLU SYND	1	1	1.3	2	1	1.3	3	2	1.3
REACT AGGRAV	-	-	-	3	3	4.0	3	3	2.0
DIG									
GASTROENTERITIS	2	2	2.6	-	-	-	2	2	1.3
TOOTH DIS	-	-	-	1	1	1.3	1	1	0.7
RES									
PHARYNGITIS	1	1	1.3	3	3	4.0	4	4	2.6
SKIN									
ALOPECIA	1	1	1.3	-	-	-	1	1	0.7
DERM CONTACT	-	-	-	1	1	1.3	1	1	0.7
DERMATITIS	-	-	-	11	9	12.0	11	9	6.0
DESQUAMATION	-	-	-	2	2	2.7	2	2	1.3
ECZEMA	-	-	-	2	2	2.7	2	2	1.3
ERYTHEMA	-	-	-	5	4	5.3	5	4	2.6
FOLLICULITIS	2	2	2.6	-	-	-	2	2	1.3
HYPERTROPHY SKIN	1	1	1.3	-	-	-	1	1	0.7
NAIL DIS	-	-	-	1	1	1.3	1	1	0.7
PRURITUS	-	-	-	1	1	1.3	1	1	0.7
UG									
CYSTITIS	-	-	-	1	1	1.3	1	1	0.7

Table 20. Local tolerability

Results		Clobetasol (N=76)	Calcipotriol (N=75)
Cutaneous Safety Parameters			
Telangiectasis (edge):			
Baseline	Mild	2 (2.6%)	3 (4.0%)
	Moderate	1 (1.3%)	-
	Severe	1 (1.3%)	-
D28	Mild	1 (1.4%)	2 (3.1%)
	Moderate	1 (1.4%)	-
	Severe	-	-
Skin atrophy (edge):			
Baseline	Mild	1 (1.3%)	-
	Moderate	1 (1.3%)	-
	Severe	1 (1.3%)	-
D28	Mild	1 (1.4%)	-
	Moderate	-	-
	Severe	-	-
Burning (scalp):			
Baseline	Mild	4 (5.3%)	4 (5.3%)
	Moderate	1 (1.3%)	1 (1.3%)
	Severe	1 (1.3%)	-
D28	Mild	4 (5.4%)	-
	Moderate	-	1 (1.6%)
	Severe	-	2 (3.1%)

In Study RD.03.SRE.2648, there were 31 AEs reported in 27 (22.5%) subjects in the CPSH group and five in five (12.5%) in the Polytar. Skin discomfort and headache were more common in the CPSH group (Table 21). Treatment related AEs were reported in ten (8.3%) subjects in the CPSH group and one (2.5%) in the Polytar. The most common treatment related AE in the CPSH group was skin discomfort (6 subjects). There was little change in telangiectasis in either treatment group (Table 22).

Table 21. Adverse events by body system and COSTART term

Body System Classification	COSTART Preferred Term	Treatment Group: Clobetasol Shampoo (N=120) #	N	%	Polytar Liquid (N=40) #	N	%	Total (N=160) #	N	%
BODY	CHILLS	0	0		1	1	2.5	1	1	0.6
	FLU SYND	2	2	1.7	0	0		2	2	1.3
	HEADACHE	6	4	3.3	0	0		6	4	2.5
	INJURY ACCID	1	1	0.8	0	0		1	1	0.6
	PAIN BACK	1	1	0.8	1	1	2.5	2	2	1.3
	SURGICAL/MED/PROC	1	1	0.8	0	0		1	1	0.6
CV	ANGINA PECTORIS	1	1	0.8	0	0		1	1	0.6
DIG	ABSCESS PERIODONT	1	1	0.8	0	0		1	1	0.6
	GI DIS	0	0		1	1	2.5	1	1	0.6
HAL	ECCHYMOSIS	1	1	0.8	0	0		1	1	0.6
MAN	HYPERCHOLESTEREM	1	1	0.8	0	0		1	1	0.6
NER	DIZZINESS	1	1	0.8	0	0		1	1	0.6
	HYPERTONIA	1	1	0.8	0	0		1	1	0.6
RES	COUGH INC	1	1	0.8	0	0		1	1	0.6
	PHARYNGITIS	2	2	1.7	1	1	2.5	3	3	1.9
SKIN	DISCOMFORT SKIN	7	7	5.8	1	1	2.5	8	8	5.0
SKIN	PRURITUS	1	1	0.8	0	0		1	1	0.6
	PSORIASIS	1	1	0.8	0	0		1	1	0.6
	WORSE TREATED DIS	2	2	1.7	0	0		2	2	1.3

Table 22. Safety outcome measures

Results	Clobetasol Shampoo		Polytar Liquid®	
Cutaneous Safety				
Telangiectasis (0-3)	*Baseline*	*Week 4*	*Baseline*	*Week 4*
None	113 (94.2%)	107 (94.7%)	37 (92.5%)	33 (91.7%)
Mild	6 (5.0%)	6 (5.3%)	3 (7.5%)	3 (8.3%)
Moderate	1 (0.8%)	0	0	0
Skin Atrophy (0-3)	*Baseline*	*Week 4*	*Baseline*	*Week 4*
None	117 (97.5%)	112 (99.1%)	38 (95.0%)	34 (94.4%)
Mild	2 (1.7%)	1 (0.9%)	2 (5.0%)	2 (5.6%)
Moderate	1 (0.8%)	0	0	0
Burning (0-3)	*Baseline*	*Week 4*	*Baseline*	*Week 4*
None	112 (93.3%)	106 (93.8%)	35 (87.5%)	35 (97.2%)
Mild	6 (5.0%)	6 (5.3%)	5 (12.5%)	1 (2.8%)
Moderate	2 (1.7%)	0	0	0
Severe	0	1 (0.9%)	0	0
Ocular Safety Evaluation (0-3)	*Baseline*	*Week 4*	*Baseline*	*Week 4*
None	111 (92.5%)	112 (99.1%)	38 (95.0%)	36 (100.0%)
Mild	9 (7.5%)	1 (0.9%)	2 (5.0%)	0

7.3.1.2. Other studies

[information redacted]

In Study 1.CG.03.SRE.257 there were 40 TEAEs reported in 21 (35.0%) subjects. Three subjects in the CPSH groups reported burning.

In Study 1.CG.03.SRE.2620 there were no clinically significant abnormalities reported on opthalmological investigation. There were no significant changes in mean IOP. TDSS decreased in both treatment groups. There was no skin atrophy and no telangiectasis. In the CPSH groups there was one dermatological and six non-dermatological AEs and in the Dermoval/Temovate groups there were two dermatological and five non-dermatological AEs. The most commonly reported AE in the CPSH group was headache (reported in four subjects).

In Study RD.06.SRE.18070 AEs were reported in three (32.1%) subjects. In addition, one subject had HPA axis suppression.

In Study 1.CG.03.SRE.2591 there was one AE reported in each of the CPSH groups and nine in four (26.7%) subjects in the Daivonex.

In Study 1.CG.03.SRE.2578 there were three AEs reported in two (18.2%) subjects in the CPSH 10 min application group, two in two (18.2%) in each of the 5 min and 2.5 min groups, and one in one (9.1%) in each of the vehicle and Ketoderm. Burning was reported in 90% of subjects in each treatment group.

7.3.2. Deaths and other serious adverse events

7.3.2.1. Pivotal studies

[information redacted]

In Study RD.06.SRE.18075 there were two SAEs in the vehicle group: asthmatic bronchitis and elevated temperature. There were no deaths.

In Study RD.03.SRE.2665, Study RD.06.SRE.18076, Study RD.03.RDE.2638 and Study RD.03.SRE.2648 there were no SAEs or deaths reported.

7.3.2.2. Other studies

[information redacted]

In Study 1.CG.03.SRE.2577 there was one SAE: amygdalectomy. There were no deaths.

In Study 1.CG.03.SRE.2620 there was one SAE in the Dermoval/Temovate group: appendicectomy. There were no deaths.

In Study 1.CG.03.SRE.2591 there was one SAE in the CPSH 15 min dry application group: knee surgery considered to be unrelated to treatment. There were no deaths.

There were no SAEs or deaths reported in Study RD.06.SRE.18070 or Study 1.CG.03.SRE.2578.

7.3.3. Discontinuation due to adverse events

7.3.3.1. Pivotal studies

[information redacted]

In Study RD.06.SRE.18075 there were two DAEs in the CPSH group (asthma and oedema of skin) and one in the vehicle (local irritation on the scalp).

In Study RD.03.SRE.2665 there was one (5.0%) subject in the vehicle group with DAE: facial oedema.

In Study RD.06.SRE.18076, one (1.1%) subject in the CPSH group discontinued due to an AE: urticarial allergic reaction to chest, considered to be unrelated to study treatment.

In Study RD.03.RDE.2638, no subjects in the CPSH and seven subjects in the calcipotril group discontinued because of AEs.

In Study RD.03.SRE.2648, there was one (0.8%) subject that discontinued because of an AE (itching and burning of the scalp).

7.3.3.2. Other studies

[information redacted]

There were no DAEs in Study 1.CG.03.SRE.2577 or Study RD.06.SRE.18070.

In Study 1.CG.03.SRE.2620, in scalp psoriasis subjects treated with CPSH there were no DAEs, but DAE was reported in one subject in the seborrhoic dermatitis subjects treated with CPSH: proctorrhagia. DAE was reported for two subjects treated with Dermoval / Temovate : moderate fever and appendicectomy (also reported as a SAE).

In Study 1.CG.03.SRE.2591 there were two (13.3%) subjects in the Daivonex group that discontinued due to AE.

In Study 1.CG.03.SRE.2578 there was one DAE in the vehicle group.

7.4. Studies of application site tolerability

[information redacted]

Study 1.GUS.04.SRE.18032 was a single centre, randomised, controlled, evaluator blinded, intra-individual comparison of contact irritation and sensitisation potential of shampoo vehicles, designed as a repeat insult patch study. The study included healthy male or female volunteers; at least 18 years of age or older; and with any skin type or of any race provided the degree of skin pigmentation did not interfere with the reading of skin reactions. The study treatments were:

a. Shampoo vehicle 662.064P, undiluted, applied on 9 cm^2 without occlusion
b. Shampoo vehicle 662.064P, 5% dilution, applied using occlusive patches
c. Shampoo vehicle 662.066P, undiluted, applied on 9 cm^2 without occlusion
d. Shampoo vehicle 662.066P, 5% dilution, applied using occlusive patches
e. White petrolatum, 0.1 g applied to each patch site using occlusive dressings

The treatments were applied for 48 hours three times per week for 3 weeks. The study comprised a 23 day treatment period and a total study duration of 6 weeks. The outcome measures were:

- Irritation response during the induction phase (a 5-point scale ranging from 0 = no reaction to 4 = intense erythema with oedema, vesicles and erosion). The cumulative irritancy index for each subject was the average score
- Sensitisation response during the sensitisation phase (a 5-point scale ranging from 0 = none to 4 = erythema with large vesiculo-bullous reaction). Sensitisation was defined as a reaction score of 2 or greater
- AEs

There were 219 subjects enrolled in the study, 210 completed, 217 were analysed for irritancy, and 210 were analysed for sensitisation. Nine subjects discontinued, none due to AE. There were 192 (87.7%) females, 27 (12.3%) males, the age range was 19 to 74 years; and 212 (96.8%) subjects were white. The mean cumulative irritancy index was 0.62 for Shampoo vehicle 662.064P and 0.64 for Shampoo vehicle 662.066P. There were no sensitisation reactions, but 29 subjects had a reaction score of 1 or greater at the 72 hour evaluation. There

were six AEs: back pain (2), headache (2), dental work, and allergy. There were no AEs related to test material, no SAEs, no deaths and no DAEs.

7.5. Laboratory tests

7.5.1. Pivotal studies

[information redacted]

In Study RD.06.SRE.18075 two subjects in the CPSH group had post-baseline elevations in serum glucose concentrations. There were no other clinically significant abnormalities in laboratory tests.

In [information redacted] Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070 there were no clinically significant laboratory test abnormalities reported.

Clinical laboratory tests were not performed in [information redacted], Study RD.03.SRE.2665, Study RD.06.SRE.18076, Study 1.CG.03.SRE.2591, Study RD.03.RDE.2638, Study RD.03.SRE.2648 or Study 1.CG.03.SRE.2578.

7.6. Post-marketing experience

Periodic Safety Update reports were provided for clobetasol propionate that covered the time period 29th June 2005 to 28th February 2011. Summary bridging reports were provided that covered the time period 17th March 2003 to 28th February 2010.

The international birth date of clobetasol propionate was stated to be 21st February 1975. It is stated that clobetasol propionate products are marketed in 50 countries and that no action has been taken for safety reason either by the Market Authorisation Holder or any Regulatory Authority. Clobetasol propionate is available in six dosage forms: scalp lotion/emulsion/lotion, gel, shampoo, spray, cream and ointment; and in one strength: 0.05%.

During the time period 17th March 2003 to 16th September 2008 the Sponsor estimates that 1751157 patients were exposed to clobetasol propionate products. During this time there were nine reports of serious/unlisted AEs, six of which were medically confirmed. During the 3 year period 29 December 2006 to 28th February 2010, 4162826 units were sold with a corresponding patient exposure of 1970775. There were 240 spontaneous reports of which ten were serious and unlisted. There were five spontaneous reports of serious/unlisted medically confirmed AEs. As of 28th February 2010 the sponsor reports 13 spontaneous reports of serious/unlisted medically confirmed AEs. From these reports glaucoma and Cushing's syndrome appear to be risks.

During the time period 1st March 2010 to 31st August 2010 nearly [information redacted] units of clobetasol products were sold by Galderma corresponding to an estimated patient exposure of [information redacted] patient treatments. There were a total of 33 spontaneous case reports, of which one was serious/unlisted: therapeutic abortion due to potential teratogenic effects of Clobex shampoo.

During the period 1st September 2010 to 28th February 2011 nearly [information redacted] units of clobetasol products were sold by Galderma corresponding to an estimated patient exposure of [information redacted] patient treatments. There were 43 spontaneous reports, eleven of which were medically confirmed and two of which were serious and unlisted: shortness of breath and Cushing's syndrome. The Cushing's syndrome occurred following 7 months of continuous treatment of Clobex shampoo at a frequency of daily to three times a week.

7.7. Evaluator's overall conclusions on clinical safety

There were slightly more AEs reported with CPSH than with vehicle with the excess appearing to be related to skin discomfort (Study RD.06.SRE.18076). There were significantly fewer subjects reporting AEs with CPSH than with calcipotriol: 10.5% compared with 30.7% respectively (Study RD.03.RDE.2638). However there was a higher proportion of subjects with AEs in comparison with Polytar: 22.5% compared with 12.5% respectively, with the excess appearing to be due to skin discomfort and headache (Study RD.03.SRE.2648).

There were few SAEs, none attributable to study treatment, and no deaths reported in the studies of CPSH. Withdrawal due to AE was uncommon.

CPSH had good dermal tolerability. It caused slight irritation only and was not a sensitiser.

There were few abnormal laboratory test results, and none attributed to CPSH, but for most of the studies routine laboratory tests were not performed.

7.7.1. Post-marketing data

Glaucoma and Cushing's Syndrome appear to be rare risks associated with treatment with clobetasol propionate. Cushings Syndrome as a result of clobetasol propionate treatment may be related to prolonged usage, well in excess of the Sponsor's recommendation.

7.7.2. General comments

The duration of follow-up from the studies was at most 2 weeks after treatment cessation, with total observation duration of 6 weeks. This was insufficient duration to evaluate rebound effects. There were also no data examining repeated short term use [information redacted] or CPSH. However, the post-marketing data did not indicate long-term adverse effects, excepting those associated with prolonged, inappropriate use.

The "Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis" recommend efficacy and safety studies of one year duration for intermittent or prolonged use. However, it is not clear how these guidelines should be applied to a treatment that is for a maximum of 4 weeks.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

CPSH was superior to vehicle in the treatment of scalp psoriasis. In Study RD.06.SRE.18075, CPSH was superior to vehicle for the primary efficacy outcome variable, Global Severity score, with success reported in 28 (28.3%) subjects in the CPSH group and five (10.2%) in the vehicle, $p = 0.012$. In Study RD.03.SRE.2665, CPSH was superior to vehicle by the Total Severity score, $p < 0.05$. In Study RD.06.SRE.18076, CPSH was superior to vehicle by the analysis of primary efficacy outcome measure, Global Severity Score. At Week 4 endpoint, 40 (42.1%) subjects in the CPSH group and one (2.1%) in the vehicle had treatment success. At Week 6, 21 (23.9%) subjects in the CPSH group still had treatment success.

CPSH was non-inferior to clobetasol propionate 0.05% gel for the treatment of scalp psoriasis. In Study RD.03.SRE.2665, non-inferiority was demonstrated in the per-protocol population and confirmed in the ITT. The 95% CI for the difference in treatments in change in Total Severity Score from baseline (Dermoval - CPSH) was 0.25 to 1.29 for the per-protocol population and 0.24 to 1.34 for the ITT. However, for some of the secondary efficacy outcome measures, clobetasol propionate 0.05% gel was superior to CPSH (Study RD.03.SRE.2665).

CPSH was superior to Calcipotriol solution 0.005%, (Dovonex/ Daivonex), twice daily, and to Polytar . In Study RD.03.RDE.2638, non-inferiority was demonstrated on the per-protocol

analysis of Total Severity Score, and superiority was demonstrated on the secondary analysis of the ITT population. The 95% CI for the difference in Day 28 Total Severity score (CPSH – calcipitriol) was -0.66 to 0.18 for the per-protocol analysis and -0.97 to -0.05 for the ITT analysis. In Study RD.03.SRE.2648, non-inferiority was demonstrated in comparison to Polytar in the per-protocol population by the predefined criteria. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar - CPSH) was -2.066 (-2.727 to -1.405), and the upper 95% CI was below the non-inferiority target of 1.5. Superiority was demonstrated by the secondary analysis of Total Severity score in the ITT population. The mean (95% CI) for the difference in Total Severity score at Week 4 (Polytar- CPSH) was -1.842 (-2.475 to -1.208), p = 0.0001.

In addition, Study 1.CG.03.SRE.2591 supported the administration method of 15 minute application to dry hair followed by lathering and rinsing.

8.2. First round assessment of risks

The risks of CPSH in the proposed usage are:

- Increased risk glaucoma and raised intraocular pressure
- HPA axis suppression
- Cushing's syndrome
- Local reactions: burning and stinging

There were slightly more AEs reported with CPSH than with vehicle with the excess appearing to be related to skin discomfort (Study RD.06.SRE.18076).

There were significantly fewer subjects reporting AEs with CPSH than with calcipotriol: 10.5% compared with 30.7% respectively (Study RD.03.RDE.2638). However there was a higher proportion of subjects with AEs in comparison with Polytar: 22.5% compared with 12.5% respectively, with the excess appearing to be due to skin discomfort and headache (Study RD.03.SRE.2648).

There were few SAEs, none attributable to study treatment, and no deaths reported in the studies of CPSH. Withdrawal due to AE was uncommon.

CPSH had good dermal tolerability. It caused slight irritation only and was not a sensitiser.

There were few abnormal laboratory test results, and none attributed to CPSH, but for most of the studies routine laboratory tests were not performed.

Exposure to Clobex shampoo in accordance with the instructions in the Product Information is unlikely to lead to significant systemic exposure to clobetasol propionate.

The shampoo formulation appeared to have less potential for HPA axis suppression, but one subject did have evidence of HPA axis suppression and treatment emergent hypertension (Study 1.CG.03.SRE.2620 and Study RD.06.SRE.18070).

8.3. Post-marketing data

Glaucoma and Cushing's Syndrome appear to be rare risks associated with treatment with clobetasol propionate. Cushings Syndrome as a result of clobetasol propionate treatment may be related to prolonged usage, well in excess of the Sponsor's recommendation.

8.4. First round assessment of benefit-risk balance

The benefit-risk balance of clobetasol propionate shampoo (Clobex shampoo), given the proposed usage, is favourable.

9. First round recommendation regarding authorisation

Clobex Shampoo should be approved for the indication of:

Topical treatment of moderate to severe scalp psoriasis in adults.

Therapeutic Goods Administration

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