Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY:	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT:		
NAME OF ACTIVE INGREDIENT(S):		

Title of study:	Clinical Efficacy Evaluation of a Fixed Combination of Calcitriol 3 µg/g with Three Concentrations (100, 250, 500 µg/g) of Clobetasol Propionate as Spray Formulation Using the Modified Dumas-Scholtz Psoriasis Mini Plaque Test under Non-Occlusive Conditions.
Investigator:	
Study centre:	
Clinical phase:	2a
Period of study (years):	March – May 2007
(date of first enrolment):	5 March 2007
(date of last subject completed):	14 May 2007
Publication(s):	
Study objective(s):	To evaluate the clinical efficacy of a fixed combination of calcitriol 3µg/g with three concentrations (100 µg/g, 250 µg/g, 500 µg/g) of clobetasol, by evaluation of their clinical efficacy in comparison to: •The same concentration of clobetasol alone in the fixed combination vehicle (clobetasol monad); and to •Two marketed products: - Dermoval® cream (clobetasol propionate 500 µg/g) as representative of the ultra-potent corticosteroids (Class I in the US classification); - Daivobet® ointment (Calcipotriol 50 µg/g / betamethasone dipropionate 500 µg/g), the first fixed combination registered in the treatment of psoriasis, which contains a class II corticosteroid (betamethasone dipropionate).
Methodology:	Single-centre, randomized, investigator blinded, active controlled, intra-individual comparison study.
Number of subjects (planned and analyzed):	32 subjects were planned; 36 were screened; and 31 were enrolled and analysed.
Diagnosis and inclusion criteria:	Men or women, at least 18 years of age, presenting stable plaque psoriasis for at least 14 days prior to baseline with target plaques of the same global severity.

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Test Product Dosage Form, route of administration, dosage regimen and (Formulation-Batch number)	50µl of each once daily non-occlusive topical application once daily, except Saturdays and Sundays, for a total of 20 applications, as follows: Fixed-combination: 3 + 100 = Calcitriol 3 µg/g + Clobetasol 100 µg/g (Formulation-Batch: 0735.1026-2F1) 3 + 250 = Calcitriol 3 µg/g + Clobetasol 250 µg/g (Formulation-Batch: 0735.1006-2F1) 3 + 500 = Calcitriol 3 µg/g + Clobetasol 500 µg/g (Formulation-Batch: 0735.0177-2F1) Clobetasol propionate monads: 100 = Calcitriol 0 µg/g + Clobetasol 100 µg/g (Formulation-Batch: 0735.1025-2F2) 250 = Calcitriol 0 µg/g + Clobetasol 250 µg/g (Formulation-Batch: 0735.1008-2F1) 500 = Calcitriol 0 µg/g + Clobetasol 500 µg/g (Formulation-Batch: 0735.1009-2F2)
Duration of treatment	Four weeks
Reference Therapies, route of administration, dosage regimen and (Batch number)	Dermoval® Cream: Clobetasol propionate 500 µg/g (Batch: C276537 and C284990) Daivobet® Ointment: Calcipotriol 50 µg/g + Betamethasone dipropionate 500 µg/g (Batch: EA7980)
Criteria for evaluation:	
Efficacy:	**Efficacy variables:** •Erythema (scored on a 0 (absent) to 4 (very severe) scale) •Scaling (scored on a 0 to 4 scale) •Infiltration (scored on a 0 to 4 scale) •Clearing score (scored on a 0 to 2 scale) **Analysed variables:** Primary criterion: •Area Under the Curve (AUC) from Day 1 to Day 29 of Total Sum Score (TSS), i.e. : sum of individual scores of erythema, scaling and infiltration Secondary criteria: •AUC of individual scores of erythema, scaling, infiltration •Time to partial clearance (Earliest time where Clearing score ≤ 1) •Time to complete clearance (Earliest time where Clearing score = 0)
Safety:	Adverse event recording at each visit

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Principal statistical methods: The AUC of the TSS (sum of individual clinical scores erythema, infiltration, and scaling), as well as those of each individual clinical score were to be calculated from Day 1 (before application) up to Day 29 by subject and by treatment, using the trapezoidal rule. Descriptive summaries of the percent reduction from baseline over time of the TSS were performed. The distribution of residuals from the analysis of variance of the AUC of the TSS was investigated to determine the presence of outliers. The areas under the curve in the PP population were to be submitted, to analyses of variance including subject, zone and treatment as factors in the model. The Tukey multiple comparison test was to be used to classify all products. Only one Tukey for multiple comparison tests was to be performed at a 5% two-sided level to classify the AUC but its interpretation was to be done on a stepwise manner.

The primary analyses compared each spray of fixed-combination versus their monad and compared each spray of fixed-combination with Daivobet® ointment.

Efficacy and Safety Results:

Subject Population:

Enrolled:	N = 31
Males/Females:	21 (67.7%) / 10 (32.3%)
Age (years, mean/range) :	52.9±11.0 /25,73
Discontinued	0
Completed the Study	N = 31
Evaluable for Efficacy:	N = 31
Evaluable for Safety:	N = 31

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Efficacy Parameters:

	Fixed-Combination (µg/g)			Daivobet®	Dermoval®	Clobetasol Propionate Monad (µg/g)		
	3 + 100	3 + 250	3 + 500			100	250	500
N	31	31	31	31	31	31	31	31
AUC Means ± SD *(the lower score, the higher the efficacy)*								
TSS	128.8±37.53	113.3±41.43	108.4±40.00	81.46±28.23	120.8±47.65	136.3±38.76	117.5±41.03	106.9±43.29
Erythema	52.29±14.28	47.12±17.20	44.68±17.17	42.94±17.83	50.61±17.88	54.02±14.28	46.32±18.15	43.22±18.09
Scaling	35.72±12.81	29.95±14.04	29.11±13.95	15.52±6.75	33.19±18.18	38.17±13.70	31.52±11.57	28.12±14.36
Infiltration	40.82±13.66	36.23±13.10	34.58±13.55	23.01±9.79	36.98±15.13	44.06±13.27	39.68±13.89	35.56±14.44
TSS Day 29	2.35±2.00	2.06±1.73	1.89±1.83	1.42±1.35	2.34±2.08	3.00±2.02	2.05±1.67	1.73±1.68
Clearance (%)								
Partial	21 (67.7)	24 (77.4)	26 (83.9)	30 (96.8)	24 (77.4)	17 (54.8)	25 (80.6)	27 (87.1)
Complete	16 (51.6)	17 (54.8)	20 (64.5)	27 (87.1)	20 (64.5)	11 (35.5)	17 (54.8)	22 (71.0)

Primary Criterion at Day 29:

Mean TSS: There was a significant difference between treatments for the AUC of the TSS ($p<0.0001$). None of the tested combination sprays were significantly more effective than their respective monad in treating psoriasis, as assessed by AUC of TSS. The fixed-combination 3+250 and 3+500 sprays were numerically more effective than Dermoval® cream but were significantly less effective than Daivobet® ointment. In addition, Daivobet® ointment was significantly more effective than all other tested products, including Dermoval® cream. Lastly, the fixed-combination 3+100 and 3+250 sprays were numerically more effective than their respective clobetasol propionate monad sprays.

Secondary Criteria at Day 29:

TSS Over Time: The mean TSSs were similar at Baseline and were around 8 for each treated area. By Day 29, all treatments were effective with reductions in TSS compared to Baseline ranging from 62.3% for the clobetasol propionate monad 100 µg/g spray to 82.2% for Daivobet® ointment. The three most effective products in decreasing order of effectiveness were Daivobet® ointment (1.42), the clobetasol propionate monad 500 µg/g spray (1.73), and the fixed-combination 3+500 spray (1.89). The fixed-combination 3+250 and clobetasol propionate monad 250 µg/g sprays were similarly effective with a mean score around 2.05 (approximately 74% reduction from Baseline). Fixed-combination 3+100 spray and Dermoval® cream were less effective with mean TSSs of 2.35 and 2.34, respectively. The clobetasol propionate monad 100 µg/g spray was the least effective product for treating psoriasis (mean TSS = 3.00).

Mean Scores of Erythema: There was a significant difference between treatments for the AUC of erythema ($p<0.01$). None of the fixed-combinations were significantly more effective than their respective clobetasol propionate monad sprays in reducing erythema. Fixed-combination 3+250 and 3+500 sprays were numerically, but not significantly, more effective than Dermoval® cream. Both products were also numerically, but not significantly, less effective than Daivobet® ointment. The fixed-combination 3+100 spray was numerically, but not significantly, less effective than Dermoval® cream and Daivobet® ointment.

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Mean Scores of Scaling:	There was a significant difference between treatments for the AUC of scaling ($p<0.0001$). None of the fixed-combination sprays were significantly more effective than their respective clobetasol propionate monads in reducing scaling. However, the fixed-combination 3+100 and 3+250 sprays were numerically more effective compared with their respective clobetasol propionate monads. All fixed-combinations were significantly less effective than Daivobet® ointment. Although the fixed-combination 3+250 and 3+500 sprays were numerically more effective than Dermoval® cream, the fixed-combination 3+100 spray was numerically less effective
Mean Scores of Infiltration:	There was a significant difference between treatments for the AUC of infiltration ($p<0.0001$). All the fixed-combination sprays were numerically, but not significantly, more effective than their respective clobetasol propionate monads in reducing infiltration. All fixed-combinations were significantly less effective than Daivobet® ointment. Although the fixed-combination 3+250 and 3+500 sprays were numerically more effective than Dermoval® cream, the fixed-combination 3+100 spray was numerically less effective.
Clearance Rates at Day29:	
Partial Clearance:	The partial clearance rate with the fixed-combination 3+250 (77.4%) and 3+500 (83.9%) sprays were similar to their respective clobetasol propionate monad sprays (80.6% and 87.1%). The fixed-combination 3+100 spray had a higher partial clearance rate than its monad (67.7% vs. 54.8%, respectively). The fixed-combination 3+250 (77.4%) and 3+500 (83.9%) sprays were close to Dermoval® cream (77.4%) but all were much lower than Daivobet® ointment (96.8%).
Complete Clearance:	The complete clearance rates for the fixed-combination 3+250 (54.8%) and 3+500 (64.5%) sprays were similar to their respective clobetasol propionate monads (54.8% and 71.0%). The fixed-combination 3+100 spray had a higher complete clearance rate than its monad (51.6% and 35.5%, respectively). The complete clearance rate for the fixed-combination 3+500 spray was the same as Dermoval® cream (both 64.5%) but much lower than Daivobet® ointment (87.1%).
Safety:	Twelve subjects (38.7%) experienced 17 AEs which were primarily headache (16.1%; 5/31) and back pain (6.5%; 2/31). All other AEs were reported by no more than one subject (3.2%; 1/31). None of the AEs were serious, nor led to permanent discontinuation, and all were unrelated to treatment. There also were no clinically important changes in vital signs or physical examination findings during the study.
Conclusion	The synergistic or additive effect of calcitriol and clobetasol propionate in a fixed-combination ethanolic spray was not confirmed. All fixed-combination ethanolic sprays were shown to be safe and well-tolerated.
Date of this report:	**01 November 2007**