2. SYNOPSIS

NAME OF COMPANY: GALDERMA R&D	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT: CD4802 0.1% ointment		
NAME OF ACTIVE INGREDIENT(S): CD4802		
Title of study:	EFFICACY AND SAFETY COMPARISON OF CD4802 0.1% OINTMENT VERSUS VEHICLE IN THE TREATMENT OF TARGET LESIONS IN ADULTS WITH ATOPIC DERMATITIS	
Investigator(s):	[redacted]	
Study centre(s):	- Centre de Pharmacologie Clinique Appliquée à la Dermatologie (CPCAD), Hôpital l'Archet 2, Nice. - Unité de Recherche Clinique en Immunologie Lyon Sud (URCI-LS) Pavillon Dufour 5F, Centre Hospitalier Lyon Sud , 69310 Pierre Benite	
Clinical phase:	Phase IIa	
Period of study:		
Date of first enrolment:	23rd May 2008	
Date of last subject completed:	23rd July 2008 (End of study: 5th September 2008)	
Publication(s):	NA.	
Study objective(s):	Efficacy objective: To evaluate the efficacy of CD4802 0.1% ointment applied once a day over four weeks versus vehicle in adult patients with atopic dermatitis. Safety objective: To evaluate the local and systemic safety of CD4802 0.1% ointment applied once a day over four weeks versus vehicle in adult patients with atopic dermatitis. Other objectives: characterise the pathology and response to treatment with proteomic and genomic analyses conducted on skin strippings and saliva samplings respectively.	
Methodology:	Multicentre, randomised, intra-individual (right versus left), vehicle controlled, double-blind study.	
Number of subjects (planned and analyzed):	Twenty subjects were planned; following blinded observations on the first 12 subjects, it was observed that 7 subjects presented a flare of eczema and/or irritation on only one side with aggravation of different signs of scoring. An interim analysis was then decided on these 12 subjects. Enrolments were frozen and the decision was taken to stop the study following this analysis.	
Diagnosis and Inclusion criteria:	Healthy males and females of non-childbearing potential, over 18 years of	

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	age, with two symmetric plaques of atopic dermatitis on each side of the body of similar severity.	
Test Product Dosage Form:	**CD4802**	
Route of administration:	Topical.	
Dosage regimen:	3 mg/cm² (Maximum 90 mg) at 0.1% once daily	
Batch/formulation number:	CD4802 ointment	
Treatment duration	4 weeks (24 applications).	
Reference Therapy	**Vehicle.**	
Route of administration	Topical.	
Dosage regimen	3 mg/cm² (Maximum 90 mg) once daily	
Batch/formulation number:	Ointment	
Treatment duration	4 weeks (24 applications).	
Efficacy assessment:	At D1, D8, D15, D22 and D29 visit during the treatment period assessment of: - Individual scores of erythema, excoriation, oedema/papulation, oozing/crusting and lichenification of target areas (on a 0 to 3 scale) - Pruritus (on a 0 to 100 mm visual analog scale) and clearing score - Subject's and Investigator's preference at D29 (left versus right side)	
Efficacy Criteria:	**Primary efficacy analysis variable:** Total Sum Score (TSS): Sum of erythema, excoriation, oedema/papulation, oozing/crusting and lichenification of target areas. **Secondary efficacy variables:** - Individual scores of erythema, excoriation, oedema/papulation, oozing/crusting and lichenification of target areas (on a 0 to 3 scale). - Pruritus assessed on a 0 to 100 mm visual analog scale - Clearing score - Subject's and Investigator's preference (left versus right side)	
Safety:	- Adverse event recording at each visit - Vital signs - Physical examination	

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	- Laboratory blood biochemistry and haematology - Calcium/creatinine ratio (2-hour urine collection)	
Other measurements:	- Genomic analysis on saliva - Proteomic Analysis on tape strippings	
Principal statistical method(s):	**1. Primary efficacy analysis** The main criterion was the Area under the curve (AUC) of Total Sum Score (sum of individual clinical scores: erythema + excoriation + oedema/papulation + oozing/crusting + lichenification) calculated from Baseline up to D29 compared via a Student t-test for paired data at a 5% significance level. **2. Secondary efficacy analysis** - Percent change from baseline in TSS was compared using a Wilcoxon Rank Signed test - AUC for each Individual clinical score from Baseline up to Day 29 were analyzed similarly as the AUC of Total Sum Score. - Change from baseline in pruritus score. - The time to complete clearing and time to partial clearing based on the the clearing score. - Investigator's and Subject's preferences analyzed using a sign test. **3. Safety analysis** Incidence of AEs, local tolerance, vital signs and laboratory parameters summarised by descriptive statistics.	

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SUMMARY	
DEMOGRAPHIC DATA	
Screened (ICF signed)	12
Screened (CRF filled in)	12
Enrolled	12
Males/Females Females Males	 0 (0.0%) 12 (100%)
Age (mean/range)	36.8±13.6 / 18.0 to 56.0 years old
Race Caucasian Black Asian Other	 9 (75%) 1 (8.3%) 1 (8.3%) 1 (8.3%)
Discontinued	0 (0%)
Medical reason	0 (0%)
Non-medical reason	0 (0%)
Lost to follow-up	0 (0%)
Completed the Study	12 (100.0%)
Assessable for efficacy	12 (100.0%)

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SUMMARY

RESULTS

Efficacy (PP = ITT)

Primary criterion:
AUC of the TSS calculated from Day 1 to Day 29 by the trapezoidal rule.

N=12			
	CD4802	VEHICLE	VEHICLE-CD4802
Mean±STD	206.8 ± 79.24	124.8 ± 55.57	-82.0 ± 70.31
Median	236.3	119.0	-85.8
Min~Max	42.0~ 297.5	38.5~ 203.0	-172~ 31.5
p-value			0.0020

p-value are based on the t-test for paired data

Secondary criteria:
Percent change from baseline in TSS

N=12			
	CD4802	VEHICLE	VEHICLE-CD4802
Mean±SD	-12.1 ± 43.68	-58.0 ± 30.71	-45.9 ± 41.97
Median	-7.69	-52.3	-52.8
Min;Max	-100; 66.7	-100; 0.0	-129; 0.0
p-value			0.0039

AUC for each Individual clinical score from Baseline up to D 29 by subject and by treatment, using the trapezoidal rule

N=12			
	CD4802	VEHICLE	VEHICLE-CD4802
Mean			
Erythema	49.00	27.71	-21.3
STD	*15.51*	*9.95*	*15.97*
p-value			0.0007
Oedema/papulation	42.00	32.08	-9.92
STD	*15.58*	*13.42*	*13.58*
p-value			0.0280
Excoriation	26.54	17.50	-9.04
STD	*20.86*	*17.40*	*15.61*
p-value			0.0701
Lichenification	45.50	31.50	-14.0
STD	*19.23*	*15.86*	*14.08*
p-value			0.0055
Oozing/crusting	43.75	16.04	-27.7
STD	25.35	14.50	21.08
p-value			0.0008

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Change from baseline in pruritus scored by treatment

		CD4802	CD4802	VEHICLE	VEHICLE-CD4802
DAY29	N	12	12	12	
	Mean±SD	-19.3±34.41	-32.3±25.91	-13.0±23.25	
	Median	-15.0	-27.5	-10.0	
	Min;Max	-65.0; 60.0	-75.0; 10.0	-65.0; 15.0	
	p-value			0.0889	

p-value are based on the Wilcoxon rank signed test

Preference by investigator

	Total	p-value
N	12 (100%)	0.0391
CD4802 side better than VEHICLE Side	1 (8.3%)	-
Efficacy identical on both sides	3 (25.0%)	-
VEHICLE side better than CD4802 Side	1 (8.3%)	-
VEHICLE side much better than CD4802 Side	7 (58.3%)	-

Preference by the subject

	Total	p-value
N	12 (100%)	0.0654
CD4802 side better than VEHICLE Side	2 (16.7%)	-
Efficacy identical on both sides	1 (8.3%)	-
VEHICLE side better than CD4802 Side	1 (8.3%)	-
VEHICLE side much better than CD4802 Side	8 (66.7%)	-

Time to Complete clearing

	CD4802	VEHICLE
N	12	12
CC at day 8 and not before	1 (8.3%)	0 (0%)
CC at day 15 and not before	0 (0%)	2 (16.7%)
CC at day 22 and not before	0 (0%)	1 (8.3%)
No CC at any time	11 (91.7%)	9 (75.0%)

Time to Partial clearing

	CD4802	VEHICLE
N	12	12
PC at day 8 and not before	5 (41.7%)	9 (75.0%)
PC at day 15 and not before	2 (16.7%)	1 (8.3%)
PC at day 22 and not before	0 (0%)	2 (16.7%)
No PC at any time	5 (41.7%)	0 (0%)

Other measurements: See reports in appendix

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- Genomic analysis on saliva - Proteomic Analysis on tape strippings	

SAFETY

	CD4802 (n=12)	**Vehicle (n = 12)**
■ Mean quantity of drug intended to be applied	3 mg/cm^2 (per application)	3 mg/cm^2 (per application)
■ Adverse Events (AEs):	18 in 10 subjects (83.3%)	9 in 6 subjects (50.0%)
■ Deaths (total):	0 (0%)	0 (0%)
■ Other serious adverse events (total):	0 (0%)	0 (0%)
■ Subject discontinuations due to AE (total):	0 (0%)	0 (0%)
■ Local tolerance: All dermatological AEs	11 in 8 (66.7%) Eczema: 6 subjects (50%) Dermatitis contact: 2 subjects (16.7%) Skin depigmentation: 2 subjects (16.7%) Skin irritation: 1 subject (8.3%)	2 in 2 (16.7%) Eczema: None Dermatitis contact: 2 subjects (16.7%) Skin depigmentation: None Skin irritation: None
■ AE related to study drug:	10 in 9 subjects (75.0%)	1 in one subjects (8.3%)
■ Dermatological AE related to study drug:	9 in 8 subjects (66.7%)	No related dermatological AE
■ Vital signs, physical examination and Laboratory parameters:	- Two subjects who were within the normal range before treatments had Adjusted calcium values below the normal range at Day29/Final visit. - One subject ([redacted]) who was below the normal range at screening had a value above the normal range at Day29/final for calcium/creatinine ratio in urinalysis. This adverse event was reported as treatment related.	

Safety Results summary

Due to the occurrence of AEs of irritation and/or worsening of eczema on only one side with aggravation of different signs of scoring, in seven subjects out of 12, an interim statistical analysis was performed on the first 12 subjects completed. This analysis aimed at providing preliminary results in order to reach a decision about the relevance of including the last eight patients as planned initially in the protocol, thus the sponsor assumed that the data already collected were to be sufficient to justify stopping the study at 12 subjects for futility.
The interim t-statistic for AUC (TSS) was in favour of the Vehicle, the probability of final significance for n=20 was virtually zero. There was no value in continuing the study. The trial was stopped with the 12 subjects already completed.

Concerning the safety, throughout the study, 10 (83.3%) subjects reported 18 AEs .Ten AEs were related to the tested product CD4802 0.1% among which 9 were dermatologic AEs and one was increase calciuria .
Out of 9 dermatologic related AEs (among 8 Subjects, 66.7%) observed for CD4802 0.1%, 6 were “flare of eczema” or “flare of eczema or irritation” on target lesion, 2 were depigmentation of elbow fold and one was an irritation on target lesion.
All these dermatological related AEs (9) were reported as mild to moderate in severity and did not lead to treatment discontinuation. They all resolved with no residual effects.

One subject ([redacted]) had increase of calciuria between screening visit (calcium creatinine ratio 0.20) and Day 29 (0.69) for a normal range between 0.30 and 0.45. This increase was classified as moderate and considered by the investigator to be related to the study treatment. No treatment was prescribed. Calciuria was controlled 21 days later on 24 hours urines, at 4.59 mmol/24h (within the normal range). This Adverse event was resolved with no residual effects.

No other clinically significant abnormality was seen and reported for the analyzed laboratory data concerning calcium metabolism parameters (corrected serum calcium) for each Subject throughout the study. No hypercalcaemia was reported.

No Serious Adverse Event was reported. No sensitization reaction observed.

CONCLUSION

This Right/Left, blinded, randomized study was stopped for futility after an interim analysis. This analysis was performed on the 12 completed subjects and before recruiting the remaining 8 ones.

The final analysis showed that the TSS in terms of AUC, but also in terms of percent change from baseline, 4 out of 5 AUC of the individual scores (Erythema, Oedema/Papulation, Oozing/Crusting and Lichenification) were significantly different in favour of the Vehicle (all $p<0.04$). The investigator’s preference was also in favour of the Vehicle ($p<0.04$). Despite showing no difference Pruritus and Subjects’ preference were in favour of the Vehicle.

Seven AEs were identified [redacted], corresponding to irritation and/or concomitant worsening of Atopic Dermatitis on one side only and which also corresponded to worsening of primary efficacy criterion (TSS, sum of 5 signs).

Moreover all the nine related dermatological AE experienced by eight subjects were on the CD4802 treated side whereas there were none on the Vehicle treated side. There were no serious adverse events in this study.