Clinical Study Synopsis for Public Disclosure

These results are supplied for informational purposes only in the interest of scientific disclosure. The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups. This information is not intended to substitute for informed medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a Healthcare Professional. Before prescribing any product mentioned in this Register, Healthcare Professionals should always refer to the specific approved product labeling information in their country. The results from a single trial may not reflect the overall results and need to be considered in the context of the totality of the available clinical research results for a product.

1. TITLE PAGE

<table>
<tr><td colspan="3">Title of Study
EXPLORATORY PHASE IIA STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CD07387 SOLUTION IN PATIENTS WITH VITILIGO</td></tr>
<tr><td>Project Name
CD07387</td><td>Project Number
253</td><td>Clinical Phase
Phase IIa</td></tr>
<tr><td colspan="2">Investigational Product
(name, formulation, concentration)
• CD07387 0.5% solution
• CD07387 1% solution
• CD07387 2% solution</td><td>Comparator Product
(name, formulation, concentration)
• CD07387 vehicle solution</td></tr>
<tr><td>Subject Population/Indication
Males and females (of non-childbearing potential) aged 18 to 65 years old, with a clinical diagnosis of non-segmental (generalized) symmetrical vitiligo, with stable plaques on the trunk for >3 months.</td><td>Treatment/Study Duration
The maximum study duration for one subject was 14 weeks, including a screening period of up to 4 weeks, a 6-week treatment period and a 4-week follow-up period.</td><td>Dose
10 µL of each treatment was applied once daily for 6 weeks (5 days per week).</td></tr>
<tr><td colspan="3">Design
This was an exploratory, multi-center, international, investigator-blinded, intra-individual, vehicle-controlled, randomized study.</td></tr>
<tr><td colspan="2">Study Initiation Date
(first Subject enrolled)
29 Oct 2010</td><td>Study Completion/Termination Date
(last Subject completed)
09 May 2011</td></tr>
<tr><td colspan="3">EUDRACT/IND No.: 2010-019994-13</td></tr>
</table>

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This abbreviated Clinical Study Report (aCSR) complies with the International Conference on Harmonization (ICH) E-3 and FDA guidance.

Authors:

Authors	Signature	Date
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Approvals	Signature	Date
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2. SYNOPSIS

NAME OF COMPANY: GALDERMA R&D	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT: NA		
NAME OF ACTIVE INGREDIENT(S):		
CD07387		
Title of study:	EXPLORATORY PHASE IIA STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CD07387 SOLUTION IN PATIENTS WITH VITILIGO	
Investigator(s):	Pr Jean-Paul Ortonne Pr Alain Taieb Dr Sunel Strauss Dr François Malan, replaced by Dr Reinard McPherson	
Study centre(s):	4 Centers in France and South Africa	
Clinical phase:	Phase IIa	
Period of study:		
Date of first enrolment:	29 October 2010	
Date of last patient completed:	09 May 2011	
Publication(s):	N/A	
Study objective(s):	To evaluate the local tolerance and systemic safety (by adverse event [AE] recording, physical examination [including body weight] vital signs, electrocardiograms [ECG] and laboratory safety tests) of CD07387 solution at 3 concentrations (0.5%, 1% and 2%) versus its vehicle after 6 weeks of treatment in patients with vitiligo. To assess a potential effect on pigmentation of CD07387 solution versus vehicle on vitiligo skin, and to characterize this potential pigmentation (i.e. type of pigmentation: follicular, marginal, mixte or diffuse). To quantify the melanin and determine the presence of epidermal melanocytes on zones treated with CD07387 solution versus vehicle, by skin biopsy sampling.	
Methodology:	This was an exploratory, multi-center, international, investigator blinded, intra-individual, vehicle-controlled, randomized study. Each subject received 3 concentrations of CD07387 solution (0.5%, 1% and 2%) and vehicle. The four	

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	treatments were randomized to be applied to 4 minizones on the margins of vitiligo plaque(s) on the trunk. Each treatment was applied once daily for 6 weeks (5 days per week). The study comprised a Screening visit (within 4 weeks prior to the start of treatment), a 6-week treatment period (with site visits for product application and study assessments 5 days per week) and a follow-up visit 4 weeks after the last product application. Safety was assessed by local tolerance assessments, AE recording, physical examinations (including body weight), vital signs, ECG, and laboratory safety tests. Efficacy was assessed by pigmentation assessments and colorimetry measurements. Pharmacodynamy was assessed by quantification of melanin and detection of epidermal melanocytes in skin biopsies from a subset of subjects.	
Number of subjects (planned and analyzed):	It was planned to enroll 36 subjects in order to have 32 subjects completing the study. Finally, 36 subjects were randomized and all subjects completed the study.	
Diagnosis and Inclusion Criteria:	Males and females (of non-childbearing potential) aged 18 to 65 years old, with a clinical diagnosis of non-segmental (generalized) symmetrical vitiligo. Subjects had stable plaques on the trunk for >3 months which could contain a total of 4 minizones each of 3 cm^2 (1-4 plaques), with the minizones presenting the same aspect, and $\geq$ 2cm apart.	
Treatment Groups:	Each subject received all 4 treatments, each treatment randomly allocated to be applied to a different mini-zone. The treatments were:	

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	- CD07387 0.5% solution - CD07387 1% solution - CD07387 2% solution - CD07387 vehicle	
Test Product Dosage Form:	- CD07387 0.5% solution - CD07387 1% solution - CD07387 2% solution	
Route of administration:	Topical	
Dosage regimen:	10 µl of study drug was applied per minizone (about 3 cm^2), once daily for 6 weeks (5 days per week).	
Batch/formulation number:	CD07387 0.5% solution: 10.01038 CD07387 1% solution: 10.01048 CD07387 2% solution: 10.01049	
Treatment duration	6 weeks (5 days per week)	
Vehicle Therapy	CD07387 vehicle	
Route of administration	Topical	
Dosage regimen	10 µl of study drug was applied per minizone (about 3 cm2), once daily for 6 weeks (5 days per week).	
Batch/formulation number:	10.00949	
Treatment duration	6 weeks (5 days per week)	
Safety:	Safety was assessed as follows: - Local tolerability assessment (erythema, edema and pruritus/stinging/burning assessed on 4-point scales from 0 = none to 3 = severe) daily during the treatment period (from Day 2), at the end of treatment visit (Day 40) and at the follow-up visit (Day 68±3 days) - Physical examination and vital signs (systolic and diastolic blood pressure and heart rate) at Screening, Baseline, end-of treatment visit (Day 40) and at the follow-up visit (Day 68±3 days) - Laboratory safety tests (hematology, blood chemistry and urinalysis) at Screening and at the	

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	end-of-treatment visit (Day 40) - 12-lead EGC at Screening and at the end-of treatment visit (Day 40) - AE recording throughout the study	
Efficacy assessment:	Efficacy was assessed as follows: Pigmentation assessed weekly during the treatment period (from Day 8), at the end-of-treatment visit (Day 40) and at the follow-up visit (Day 68 ±3 days) by: - Surface of pigmentation: evaluated using a 12-point scale (from 0, no pigmentation, to 11, complete pigmentation) - Contrast scale: contrast, in term of difference of pigmentation between treated zones and healthy surrounding skin assessed using a 4-point scale - Type of pigmentation: categorized as follicular, marginal, mixte, or diffuse Colorimetry: L*, *a and *b measured at the centre of each treated zone using a spectrocolorimeter at Baseline, once a week during the treatment period (starting on Day 1), at the end-of-treatment visit (Day 40) and at the follow-up visit (Day 68±3 days). Photographs (normal and UV) taken at Baseline, Day 22, the end-of-treatment visit (Day 40) and at the follow-up visit (Day 68±3 days).	
Efficacy Criteria:	**Co-primary criteria:** - Surface of pigmentation - Contrast scale assessment **Secondary efficacy criteria:** - Type of pigmentation - Colorimetry measurements	
Pharmacodynamics	Skin biopsies were performed in a subgroup of 22 subjects. The subgroup was separated into 3 groups, one for each active treatment concentration, according to biopsy numbers assigned to subjects. Each subject had two skin biopsies, one on an active zone and one	

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	on the vehicle treated zone. Melanin was quantified and epidermal melanocytes were detected. Pharmacodynamics results are presented in a separate report.	
Principal statistical method(s):	For efficacy, the surface of pigmentation at the end-of-treatment visit (Day 40) was submitted to an analysis of variance (ANOVA) (subject, zone, dose). The dose was coded 0, 1, 2, 3 and was used as a numeric covariate. The test of the dose was primarily to detect any dose-response relationship. A separate model added “treatment” to test lack of fit of the primary model. The contrast scale and the changes from baseline in colorimetry parameters were analysed using the same method. All tests were two-sided and the 0.05 probability level was chosen to declare significance.	
SUMMARY		
SUBJECT DISPOSITION AND DEMOGRAPHY		
In total, 36 subjects were randomized, and all subjects completed the study, and were included in the Intent to Treat (ITT), Per-Protocol (PP) and Safety populations. The mean (SD) age of subjects was 49.4 (11.1) years. Just over half the subjects were female (55.6%) and the majority of subjects were Caucasian (86.1%).		

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SAFETY RESULTS

The results of the safety assessments did not raise any cause for concern.

Most subjects reported no local intolerance. During the treatment period, no subjects experience edema, all reports of pruritus/stinging/burning were mild, and 2 subjects experienced transient moderate erythema on-treatment (1 each with CD07387 0.5% and 2%) during treatment period. In addition, one subject (#5140005) had mild edema on his final follow-up visit (Day 68).

A total of 45 AEs were reported in 19 subjects (52.8%). The only AEs reported in more than 1 subject were headache (4 subjects, 11.1%), nasopharyngitis (3 subjects, 8.3%) and gastroenteritis, bronchitis, and rhinitis (each in 2 subjects, 5.6%).

Only 1 event was considered to be treatment-related: severe abdominal tenderness, an AE of special interest (AESI), which was reported one day after a moderate, non-treatment related AE of gastroenteritis. Both events resolved. All other AEs were mild or moderate in severity. A mild AE of unilateral gynaecomastia right was initially reported as treatment-related by the investigator, who subsequently changed the report to non treatment-related.

Dermatologic AEs were reported in 3 subjects (8.3%), none of which were considered to be treatment-related. Zone specific events (unrelated to treatment) were skin hyperpigmentation (localized around/outside the treated minizones, reported as AESIs in 1 subject for the vehicle and CD07387 1% minizones), and sunburn (in 1 subject for the CD07387 2% minizone).

One subject experienced a serious adverse event (SAE) (dysfunctional uterine bleeding) which was not considered related to treatment. There were no AEs leading to discontinuation and no deaths.

No clinically significant abnormal biochemistry results were reported during the study. No safety concerns were highlighted by assessments of biochemistry, hematology, urinalysis, vital signs and physical examinations.
Abnormal, clinically significant ECG results were reported at the end of treatment in 1 subject.

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EFFICACY RESULTS
Primary efficacy variable:

Surface pigmentation: An ANOVA analysis showed a statistically significant dose response with CD07387 in the improvement in surface pigmentation at the end-of treatment (Day 40) (p=0.0067). There was a statistically significant difference in surface of pigmentation between vehicle and the highest CD07387 dose (2%) at the end-of treatment (Day 40) (Wilcoxon rank signed test, p=0.0097). However, the clinical relevance of the differences seen are minimal, as even in the highest CD07387 dose group, the majority of subjects (28 subjects, 78%) had surface pigmentation $\leq$ 20%.

Surface of Pigmentation by study product at the end-of-treatment (Day 40) (ITT population)

Day 40 or Early Termination/ITT	Vehicle		CD07387 0.5%		CD07387 1%		CD07387 2%	
	n	%	n	%	n	%	n	%
Total	36	100	36	100	36	100	36	100
No pigmentation (0%)	23	63.9	24	66.7	20	55.6	18	50.0
0 < pigmentation <= 10%	8	22.2	4	11.1	7	19.4	5	13.9
10 < pigmentation <= 20%	1	2.8	2	5.6	2	5.6	5	13.9
20 < pigmentation <= 30%			3	8.3	2	5.6		
30 < pigmentation <= 40%	1	2.8			3	8.3	3	8.3
60 < pigmentation <= 70%	1	2.8	1	2.8			1	2.8
70 < pigmentation <= 80%					1	2.8	3	8.3
80 < pigmentation <= 90%	2	5.6	2	5.6	1	2.8	1	2.8

n = number of subjects
Surface of Pigmentation: 12-point scale from 0 = No pigmentation to 11 = Complete pigmentation.

Contrast scale: There was no statistically significant differences in contrast scale scores between the treatments at the end-of-treatment (Day 40).

Contrast scale by study product at the end-of-treatment (Day 40) (ITT population)

	Vehicle	CD07387	CD07387	CD07387

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			0.5%		1%		2%	
	N	%	n	%	n	%	n	%
Total	36		36		36		36	
Not colorated at all (i.e. same color as the vitiligo plaque)	23	63.9	24	66.7	20	55.6	18	50.0
Colorated but clearer than surrounding healthy skin	10	27.8	7	19.4	12	33.3	13	36.1
Same color as surrounding healthy skin	3	8.3	5	13.9	4	11.1	5	13.9

Contrast Scale: 4-point scale from 0 = Not colorated at all to 3 = Darker than surrounding healthy skin.

All types of pigmentation were seen, with no difference between treatments in the type reported. Changes in colorimetry parameters were small, and there were no statistically significant differences between vehicle and active treatments.

CONCLUSIONS

CD07387 solution was well tolerated when applied to vitiligo plaques, but did not have a clinically relevant effect on plaques pigmentation after 6 weeks of treatment.

An ANOVA analysis showed a statistically significant dose response with CD07387 in the improvement in surface pigmentation at the end-of treatment (Day 40) (p=0.0067). There was a statistically significant difference in surface of pigmentation between vehicle and the highest CD07387 dose (2%) at the end-of treatment (Day 40) (Wilcoxon rank signed test, p=0.0097). However, the clinical relevance of these differences is minimal, as even with the highest CD07387 dose, the majority of subjects had surface pigmentation $\leq$ 20%. ANOVA analyses did not show any statistical significant dose response in the contrast scale and colorimetry parameters. There was no trend regarding the type of pigmentation reported.

The results of the safety assessments did not raise any cause for concern. Systemic and local tolerance of CD07387 was good.

Only 1 treatment-related AE was reported (severe abdominal tenderness). Zone specific events (unrelated to treatment) were skin hyperpigmentation (localized around/outside the treated minizones in 1 subject for the vehicle and CD07387 1% minizones), and sunburn (in 1 subject for the CD07387 2% minizone). The event of abdominal tenderness and the events of skin hyperpigmentation were AESIs. One subject experienced an SAE (dysfunctional uterine bleeding) which was not considered related to treatment. There were no AEs leading to discontinuation and no deaths.

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