Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY: Galderma	***For regulatory use only***
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): Not applicable	
EUDRACT/IND N°: 2006-003156-37	
Study Title:	AN EXPLORATORY STUDY TO EVALUATE RELAPSES FOLLOWING AN INITIAL 12 WEEKS DOSE-RANGE STUDY WITH CD5024 CREAM VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE 0.75% CREAM IN PAPULO-PUSTULAR ROSACEA – A 6 MONTHS FOLLOW-UP TREATMENT-FREE STUDY.
METHODOLOGY	
Study objective(s): To evaluate relapses in patients successfully treated in an initial Dose-range study (RD.03.SPR.40027) with CD5024 cream or its vehicle or Metronidazole 0.75% cream (Rozex®)	
Study design and clinical phase: Exploratory, multi-centre, treatment-free, and Investigator-blinded study on the assigned treatments (three different concentrations of CD5024 cream (1%, 0.3%, and 0.1%) once daily or CD5024 1% cream twice daily versus its vehicle and versus metronidazole 0.75% cream over 12 weeks over an observation period of 6 months. Study visits were performed once a month.	
Study centre(s): A total of 25 centres in Australia, the Czech Republic, Germany, Hungary, and the Russian Federation screened and randomized subjects.	
Number of subjects: Planned: 130 subjects; Enrolled: 149 subjects.	
Diagnosis and Inclusion criteria: Male or female subjects, successfully treated in an initial phase 2 dose-ranging study. Evaluation of treatment success was based on an Investigator Global Assessment scale (score 0 or 1, grade "clear" or "almost clear" on a 5-point scale) were eligible for this present follow-up study.	
Study period: From 13 October 2006 (first subject included) to 19 November 2007 (last subject completed). **Investigational products:** Not applicable	

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METHODOLOGY (Continued)

Criteria for evaluation:

- Efficacy Criteria
  - -Time to relapse, according to the three definition of the relapse:
    - Definition 1: an IGA 2 score equal or above to 2 (IGA 2 is a 5-point scale, from 0: clear to 4: severe);
    - Definition 2: a 2-point difference in the IGA 2 score compared to Baseline;
    - Definition 3: failure to maintain at least 50% of the improvement achieved at the end of the initial study RD.03.SPR.40027 (improvement was defined as the difference in total inflammatory lesion count between Baseline and Week 12);
  - Relapse rates according to the three definitions;
  - Change from Baseline in erythema score;
  - Change from Baseline in telangiectasia score;
  - Change from Baseline in Investigator's Global Assessment score 1;
  - Change from Baseline in Investigator's Global Assessment score 2;
  - Change from Baseline in inflammatory lesion counts.

- **Safety**

Recording of Adverse Events throughout the study.

Principal statistical methods:

- **Efficacy**

Subjects included in this follow-up study were part of the efficacy and safety population.

Summary tables presenting time-adjusted incidences of relapse for each definition, by group will be presented. Subjects without relapse at the end of the study and who normally completed the 6 month follow-up will be considered as censored the day of last evaluation. The procedure LIFETEST from the Statistical Analysis System (SAS) package will be used to calculate time-adjusted incidence. Kaplan Meier curves for time adjusted cumulative incidences of relapse will be presented by group.

For calculation of time adjusted incidences of relapse, two conventions will be used for subject who discontinued the study prematurely and without relapse:

- Subject who discontinues the study prematurely and without relapse will be considered as censored the day of last evaluation.
- Subject who discontinues the study prematurely and without relapse will be considered as relapse 30 days after the day of last evaluation. This second analysis is considered as sensitivity analysis

A statistical test comparing the time adjusted cumulative incidences of relapse over time between all groups will be made, using the two sided nonparametric Wilcoxon test and log rank test for survival curves.

- **Safety**

Adverse events were tabulated in frequency tables.

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RESULTS

- **Subject Disposition**

From 296 subjects enrolled in study RD.03.SRE.40027, 273 completed the study; a total of 192 subjects were eligible for study RD.03.SRE.40037.

A total of 149 subjects participated in the study. One hundred and one (101, 67.8%%) subjects completed the study.

Summary Table 1 – Subject Disposition

			CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	Metronidazole 0.75% BID	Vehicle BID	Total
	Included	n (%)	28 (100)	27 (100)	31 (100)	26 (100)	20 (100)	17 (100)	149 (100)
	Completed the study		18 (64.3)	18 (66.7)	21 (67.7)	21 (80.8)	12 (60.0)	11 (64.7)	101 (67.8)
[29-56] days	Premature discontinuation	All	1 (3.6)	2 (7.4)	2 (6.5)	-	3 (15.0)	1 (5.9)	9 (6.0)
		Other	-	1 (3.7)	-	-	-	-	1 (0.7)
		Protocol Violation	-	-	-	-	1 (5.0)	-	1 (0.7)
		Subject's Request	1 (3.6)	1 (3.7)	2 (6.5)	-	2 (10.0)	1 (5.9)	7 (4.7)
[57-84] days	Premature discontinuation	All	3 (10.7)	1 (3.7)	3 (9.7)	1 (3.8)	3 (15.0)	2 (11.8)	13 (8.7)
		Other	2 (7.1)	1 (3.7)	-	-	2 (10.0)	1 (5.9)	6 (4.0)
		Subject's Request	1 (3.6)	-	3 (9.7)	1 (3.8)	1 (5.0)	1 (5.9)	7 (4.7)
[85-112] days	Premature discontinuation	All	4 (14.3)	3 (11.1)	3 (9.7)	2 (7.7)	2 (10.0)	3 (17.6)	17 (11.4)
		Other	-	-	2 (6.5)	1 (3.8)	-	-	3 (2.0)
		Subject's Request	4 (14.3)	3 (11.1)	1 (3.2)	1 (3.8)	2 (10.0)	3 (17.6)	14 (9.4)
[113-140] days	Premature discontinuation	All	-	2 (7.4)	-	2 (7.7)	-	-	4 (2.7)
		Subject's Request	-	2 (7.4)	-	2 (7.7)	-	-	4 (2.7)
>=141 days	Premature discontinuation	All	2 (7.1)	1 (3.7)	2 (6.5)	-	-	-	5 (3.4)
		Other	-	1 (3.7)	2 (6.5)	-	-	-	3 (2.0)
		Subject's Request	2 (7.1)	-	-	-	-	-	2 (1.3)

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RESULTS (Continued)

■ **Demographics and Baseline Data**

Demographics and Baseline data of the main efficacy criteria are depicted in Summary Table 2 below.

Summary Table 2 – Demographics and Baseline Data

		CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	Metronidazole 0.75% BID	Vehicle BID	Total
Gender	**N (%)**	28	27	31	26	20	17	149
	Female	19 (67.9)	19 (70.4)	21 (67.7)	20 (76.9)	13 (65.0)	14 (82.4)	106 (71.1)
	Male	9 (32.1)	8 (29.6)	10 (32.3)	6 (23.1)	7 (35.0)	3 (17.6)	43 (28.9)
Phototype	**N (%)**	28	27	31	26	20	17	149
	I	3 (10.7)	5 (18.5)	3 (9.7)	4 (15.4)	-	1 (5.9)	16 (10.7)
	II	12 (42.9)	11 (40.7)	16 (51.6)	15 (57.7)	14 (70.0)	10 (58.8)	78 (52.3)
	III	11 (39.3)	10 (37.0)	9 (29.0)	6 (23.1)	5 (25.0)	6 (35.3)	47 (31.5)
	IV	2 (7.1)	1 (3.7)	3 (9.7)	1 (3.8)	1 (5.0)	-	8 (5.4)
Race	**N (%)**	28	27	31	26	20	17	149
	Caucasian	28 (100)	27 (100)	31 (100)	26 (100)	20 (100)	17 (100)	149 (100)
Age (in Years)	**N**	28	27	31	26	20	17	149
	Mean±SD	53.6±14.7	53.2±14.8	51.3±14.7	50.5±10.2	54.7±15.7	55.2±11.3	52.9±13.7
	Median	52	54	52	47.5	54.5	57	52
	Min~Max	31~81	20~82	23~78	27~72	20~84	31~77	20~84

Baseline disease characteristics were similar in all groups and for all clinical parameters. Mean inflammatory counts ranged from 3.3 in the vehicle group to 4.7 in the CD5024 0.1% QD and CD5024 1% BID group. Overall, the mean telangiectasia score reached 1.1; the mean erythema score was 0.8 and more than 90% of the subjects had an IGA1 of 0 or 1.

This was a treatment free exploratory study on relapse after initial topical treatment in rosacea patients. Out of the initially 273 patients who completed the initial study (RDS.03.SRE.40027), 192 across all groups were eligible showing at end of the initial study a clinical improvement defined as "clear" or "almost clear" (grade 0 or 1) on the IGA2 scale. A total of 149 subjects of those (76%) participated in the present study: 28 subjects previously treated with CD5024 0.1% QD, 27 with CD5024 0.3% QD, 31 with CD5024 1% QD, 26 with CD5024 1% BID, 20 with Metronidazole 0.75% BID and 17 with the vehicle.

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RESULTS (Continued)

With Definition 1 and Convention 1, 36 (24.8%) subjects had relapsed prior to Day 84 whatever the treatment in study RD.03.SRE.40027; this number increased up to 53 (37.9%) subjects prior to Day 168. In other terms, more than 75% of patients remained "clear" and "almost clear" three months after an initial successful treatment and more than 60% remained so even six months after the initial treatment was stopped. Using the other definitions of relapse, relapse free periods are even higher.

With Definition 1 of relapse (IGA 2 ≥ 2) on Convention Analysis 1, until Day 84, relapse free rates with CD5024 0.3% QD, CD5024 1% QD and CD5024 1% BID were higher compared to that observed with the CD5024 0.1% QD, Metronidazole 0.75% BID and CD5024 vehicle. These results suggest that subjects previously treated with CD5024 0.3% QD, 1% QD or BID tended to a delayed onset of relapse compared to subjects treated with CD5024 0.1%, vehicle or Metronidazole. 0.75% BID. However, these results were not confirmed by Definition 2 and 3 and none of the analyses were statistically significant.

With Definition 1 of relapse, Convention analysis 2 provided a ranking of the six groups similar to that obtained with Convention 1. Therefore, drop outs had little influence on the results; on the contrary, the ranking was not consistent between Conventions for both Definitions 2 and 3. This can be explained by the more demanding criterion of relapse with these 2 definitions, many drop outs occurring before the criterion can even be observed. Also, the observation that the ranking was similar across definitions when convention 2 was used can be explained by the fact that drop outs are all considered relapses with the 3 definitions, thereby tending to equalize the results whatever the definition.

Change from Baseline for IGA 1 and 2, erythema and telangiectasia scores as well as for inflammatory lesion counts were similar among groups. The EQ-5D questionnaire did not show differences among groups in this study.

The incidence of AEs ranged from 14% in the CD5024 0.1% QD and metronidazole 0.75% BID treatment group to 30% in the CD5024 0.3% QD and the vehicle group. There was no trend in an increased incidence with increasing doses. Proteinuria reported for one subject treated previously with CD5024 1% BID was the only potentially related Adverse Events.

Three subjects reported four serious adverse events, none was related to the treatments previously administered and none let to the withdrawal of the subjects. One subject treated with CD5024 0.3% QD had a moderate bunion, one previously treated with CD5024 1% BID experienced a severe secondary glaucoma secondary and a third previously treated with Metronidazole 0.45% BID reported a mild coronary artery restenosis and a mild ischemic heart disease. None of the subjects withdraw from the study.

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RESULTS (Continued)

Summary Table 3 - Overview of Subjects reporting Adverse Events

	CD5024 0.1% QD (N=28)	CD5024 0.3% QD (N=27)	CD5024 1% QD (N=31)	CD5024 1% BID (N=26)	metronidazole 0.75% BID (N=20)	vehicle QD (N=17)
	n (%) subjects	n (%) subjects	n (%) subjects	n (%) subjects	n (%) subjects	n (%) subjects
All AEs	4 (14.3)	8 (29.6)	6 (19.4)	6 (23.1)	3 (15.0)	5 (29.4)
Related AEs	0	0	0	1 (3.8)	0	0
All dermatologic AEs	0	0	0	0	0	0
Related dermatologic AEs	0	0	0	0	0	0
All serious AEs	0	1 (3.7)	0	1 (3.8)	1 (5.0)	0
Related serious AEs	0	0	0	0	0	0
AEs leading to discontinuation	0	0	0	0	0	0
Related AEs leading to discontinuation	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

CONCLUSION

More than 75% of patients stayed "clear" and "almost" clear three months after an initial successful treatment and more than 60% remained so even 6 months after the initial treatment was stopped, whatever the treatment. The study suggested that subjects successfully treated for 12 weeks with CD5024 1% may remain disease free for a longer period of time than those successfully treated with Metronidazole 0.75% BID or the CD5024 vehicle. Results tend to show that relapse based on Definition 1 is little affected by the number of drop outs. However, none of the analyses could generate statistical differences between groups in this exploratory study.