Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY:	***For regulatory use only***
Galderma R&D	
NAME OF FINISHED MEDICINAL PRODUCT:	
Not applicable	
NAME OF ACTIVE INGREDIENT(S):	
CD2027	
Title of study:	A multicenter, randomized, intra-individual, double-blinded, vehicle-controlled study to evaluate the efficacy and safety of CD2027 9 µg/g ointment applied twice daily over 4 weeks in the treatment of target lesions in adult subjects with *atopic dermatitis*

Study centers

Approximately 4 centers were planned to participate, 5 centres in Europe, 3 in France and 2 in Hungary participated and recruited subjects.

Clinical phase

Phase 2a therapeutic exploratory study

Study period

- Date of first included: 02Sep2009
- Date of last subject completed:16Nov2009

Study objectives

To evaluate the efficacy and safety of CD2027 9µg/g ointment versus its vehicle applied twice daily on target lesions, over 4 weeks of treatment in adult subjects with *atopic dermatitis*.

Study design

Multicenter, randomized, intra-individual, double blinded, vehicle controlled study.

Approximately 35 subjects were to be screened to treat approximately 28 subjects.

Diagnosis and key inclusion and non-inclusion criteria

- Key inclusion criteria
  - The subject is a male or female, 18 years of age or older (screening visit).
  - The subject has a clinical diagnosis of *atopic dermatitis* according to the Hanifin and Rajka criteria at screening and baseline visits.
  - The subject has at least 2 equivalent symmetrical target lesions of *atopic dermatitis* on comparable body areas (left/right) which (screening and baseline visits):
    - Are between 20 and 200 cm² and do not represent more than 1% of the BSA.
    - Have not more that a 2-fold difference in size.
    - Are not on hands, feet, genitalia or face.
    - Present a total severity score of at least "6/15" (total score defined as the sum of erythema, papulation/induration, oozing/crusting, excoriation, lichenification) with an erythema score of at least "2", excoriation score of at least "2" and oozing/crusting score not more than "1".
    - Are of similar severity (severity of the two target lesions does not differ by more than 1 point based on the TSS score).
    - Have a pruritus score of at least "2".
- Key non-inclusion criteria
  The subject has:
  - An additional underlying known dermatological disease, a surgical or medical condition that, in the opinion of the investigator, may confound the study assessment and might interfere with interpretation of the study results (e.g., other dermatological diseases affecting the treatment areas, such as psoriasis, severe ichtyosis, Netherton syndrome, exfoliative erythrodermia, impetiginized *atopic dermatitis*…) (screening and baseline visits).
  - An albumin-adjusted calcium above the upper normal range at the screening laboratory evaluation (baseline visit).
  - An history/signs/symptoms suggestive of an abnormality of calcium homeostasis (such as hyperparathyroidism, Paget's disease, adrenal insufficiency, hyperthyroidism…) (screening visit).
  - Signs and symptoms of urinary stones (screening visit) or had urinary stones since the past 5 year before screening visit
  - Not undergone washout periods of sufficient duration for the specified treatments at baseline (screening and baseline visits):

Test Product Dosage Form

	Investigational Product	Comparator Product
Trade Name or equivalent	Not Applicable	
Name of Drug Substance (INN)	Calcitriol	Not Applicable
Internal code	CD2027	CD2027 Vehicle
Pharmaceutical Form	Ointment	
Concentration	9µg/g	0µg/g
Packaging (type and size)	30 gram aluminum tubes	
Storage Conditions	Store below 25°C	
Dosage (total daily dose)	Maximum 800mg (Maximum 400mg per application to cover between 20 & 200 cm^2 at 2mg/cm^2)	
Dose regimen		
Route	Topical	
Frequency	Twice daily	
Duration of administration	4 weeks	
Treatment areas	Target lesions	

Efficacy assessment

- Efficacy measurements
  - Individual scores of erythema, papulation/induration, oozing/crusting, excoriation, lichenifaction, pruritus on a 4-point scale on target lesions at Day 0 (baseline) and at every following visits until Day 29/Early Termination (ET) visit.
  - Subject's and Investigator's treatment preference scale between each target lesion at Day 29/ET visit.
- Efficacy criteria
  - Primary efficacy criterion
    - Total Sum Score (TSS) on target lesion (sum of individual clinical scores of erythema, excoriation, papulation/induration, oozing/crusting and lichenification)
- Secondary efficacy criteria
  - Percent change from baseline of the TSS at each evaluation visit.
  - Success rate of target lesion (defined as all signs of the TSS equal to "0" except for erythema which could have been "0" or "1") at each evaluation visit
  - Change from baseline in individual scores of erythema, excoriation, papulation/induration, oozing/crusting and lichenification on target lesion, at each evaluation visit.
  - Pruritus score on target lesion, at each evaluation visit.
  - Change from baseline in pruritus score on target lesion, at each evaluation visit.

- Investigator's and Subject's treatment efficacy preference at Day 29/ET visit (end of treatment visit)

Safety assessment

- Adverse event at baseline and at every following visit until Day 29/ET visit
- Vital signs/Physical examination at screening, baseline and at Day 29/ET visits
- Routine laboratory blood chemistry and hematology at screening visit to allow inclusion at baseline visit and at Day 9/ET visit (non-fasting samples)
- Calcium/Phosphorus homeostasis (calcium, albumin, albumin-adjusted calcium, phosphorus) at screening to allow inclusion at baseline visit, at Day 0, at Day 08, Day 15 and Day 29/ET visits.

Pharmacodynamics

- 25OH vitamin D; 1,25 (OH)2 vitamin D and iPTH at visit Day 1 and visit Day 29/ET.

Other

- BSA affected by the disease at Baseline visit and at each following visit until Day 29/ET visit.

Principal statistical methods

The primary efficacy endpoint was the Total Sum Score on target lesion (sum of individual clinical scores of erythema, excoriation, papulation/induration, oozing/crusting and lichenification) at Day 29 (ITT-LOCF) in which the missing data at D29 in the Intent To Treat (ITT) population was imputed by the last observation carried forward (LOCF) approach.

The TSS, as well as each individual clinical score were compared between treatments using t-test for paired data.

Per protocol analyses were also performed to assess the robustness of the conclusions.

Results

- Demographics and baseline disease characteristics

Five (5) sites, 3 in France and 2 in Hungary screened 45 and treated 40 subjects.

From these 40 subjects, 34 (85%) completed the study as planned, 5 (12.5%) discontinued due to adverse events and one (1; 2.5%) terminated the study due to "condition clear".

Data from all treated subjects were included in the ITT analysis; data from 35 were included in the PP analysis, and data from 40 were included in the safety analysis.

Of the 40 subjects, 27 (67.5%) were females and 38 (95%) were Caucasians. The mean age was 32.1 years.

Table 1 Demographic Data

		ALL
Gender	**N (%)**	40
	Female	27 (67.5)
	Male	13 (32.5)
Race	**N (%)**	40
	Caucasian	38 (95)
	Hispanic	1 (2.5)
	Other	1 (2.5)
Age (in Years)	**N**	40
	<65 Years	39 (97.5%)
	>=65 Years	1 (2.5%)
	Mean±SD	32.1±12.5
	Median	27.5
	Min~Max	18~67

All subjects had at baseline on both sides a TSS of at least "6". One (1) subject had an oozing/crusting score on both sides of "3". All individual signs as well as the TSS were similar in terms of means and distributions between the 2 treated sides.

Table 2 Baseline disease characteristics (ITT population)

		CD2027	vehicle
Erythema	N	40	40
	1-Mild		1 (2.5%)
	2-Moderate	26 (65.0%)	26 (65.0%)
	3-Severe	14 (35.0%)	13 (32.5%)
	Mean±SD	2.35±0.48	2.30±0.52
	Median	2.00	2.00
	Min~Max	2.00~3.00	1.00~3.00
Excoriation	N	40	40
	0-None		1 (2.5%)
	1-Mild	22 (55.0%)	20 (50.0%)
	2-Moderate	15 (37.5%)	18 (45.0%)
	3-Severe	3 (7.5%)	1 (2.5%)
	Mean±SD	1.53±0.64	1.48±0.60
	Median	1.00	1.00
	Min~Max	1.00~3.00	0.00~3.00
Induration/Papulation	N	40	40
	1-Mild	5 (12.5%)	5 (12.5%)
	2-Moderate	27 (67.5%)	27 (67.5%)
	3-Severe	8 (20.0%)	8 (20.0%)
	Mean±SD	2.08±0.57	2.08±0.57
	Median	2.00	2.00
	Min~Max	1.00~3.00	1.00~3.00
Oozing/Crusting	N	40	40
	0-None	17 (42.5%)	17 (42.5%)
	1-Mild	22 (55.0%)	22 (55.0%)
	3-Severe	1 (2.5%)	1 (2.5%)
	Mean±SD	0.63±0.63	0.63±0.63
	Median	1.00	1.00
	Min~Max	0.00~3.00	0.00~3.00
Lichenification	N	40	40
	0-None	1 (2.5%)	1 (2.5%)
	1-Mild	12 (30.0%)	12 (30.0%)
	2-Moderate	19 (47.5%)	19 (47.5%)
	3-Severe	8 (20.0%)	8 (20.0%)
	Mean±SD	1.85±0.77	1.85±0.77
	Median	2.00	2.00
	Min~Max	0.00~3.00	0.00~3.00

Table 2 Baseline disease characteristics (ITT population)

Pruritus	**1-Mild**		1 (2.5%)
	2-Moderate	29 (72.5%)	26 (65.0%)
	3-Severe	11 (27.5%)	13 (32.5%)
TSS	**N**	40	40
	Mean±SD	8.43±1.89	8.33±1.80
	Median	8.00	8.00
	Min~Max	6~14	6~13
Area (cm^2)	**N**	40	40
	Mean±SD	63.0±34.2	63.7±35.3
	Median	51.0	50.0
	Min~Max	28.0~170	28.0~172

- Efficacy
  - Primary efficacy criterion

The total severity score (TSS) at Day 29-LOCF (ITT population) was the primary efficacy criterion.

TSS mean values were similar at baseline with "8.4" for CD2027 9µg/g ointment side and "8.3" for the vehicle side. At Day 29-LOCF, both treatments had reduced the mean TSS compared to baseline by about 36.1% and 48.2% for the CD2027 9µg/g ointment and for the vehicle, respectively.

Results at Day 29 showed that the final mean TSS with CD2027 9µg/g ointment was numerically higher (5.5 ± 3.69) than that of the vehicle (4.4 ± 4.54), although there was no statistical difference between the 2 treated sides in the ITT population. This result was confirmed in the PP analysis.

Table 3 Total sum score at Day 29

		CD2027	vehicle	CD2027-vehicle	p-value (1)
Day 29 - LOCF (ITT population)	N	40	40	40	
	Mean ± SD	5.5±3.69	4.4±4.54	1.1±4.20	0.113
	Median	5.0	3.0	1.0	
	Min~Max	0~13	0~14	-10~13	
	Q1~Q3	3~8	1~7	-1~3	
Day 29 (PP population)	N	35	35	35	
	Mean ± SD	5.1±3.35	4.2±4.42	0.9±4.23	0.224
	Median	5.0	3.0	1.0	
	Min~Max	0~13	0~14	-10~13	
	Q1~Q3	3~8	0~7	-1~2	

(1) t-test for paired data

- Secondary efficacy criteria
  - *TSS score over time*

A numerical superiority in efficacy of the vehicle over the CD2027 9µg/g ointment, in terms of percent reduction from baseline in the TSS, was observed as early as Day 8-LOCF and sustained until Day 29-LOCF (ITT population). This superiority was statistically significant at Day 8--LOCF and Day 15-LOCF (p=0.01 and p=0.043) but was no more at Day 22-LOCF and at Day 29-LOCF (p=0.076 and p=0.069).

  - *Individual signs*

At any time and for any sign, the observed differences between the two treated sides were numerically in favor of the vehicle. This difference was statistically significant for erythema at Day 29-LOCF (p=0.009).

  - *Success rate*

At Day 29-LOCF, 13 (32.5%) subjects were rated as success on the Vehicle treated side compared to 5 (12.5%) on the CD2027 9µg/g ointment side.

  - *Treatment efficacy preference*

At Day 29/Final visit, both preferences, that rated by the investigator and that rated by the subject were statistically significant in favor of the vehicle (p=0.047 for the Investigator and p=0.025 for the subject).

- Safety

Twenty-five (25; 62.5%) subjects experienced 46 adverse events on the CD2027 9µg/g ointment side and 21 (52.5%) subjects experienced 35 adverse events on the vehicle side. Related dermatological AE were more frequent on the CD2027 9µg/g ointment-treated side with 21 events reported by 17 (42.5%) of all subjects compared to 9 events reported by 6 subjects (15%) on the vehicle treated side. Twelve (12; 30%) subjects reported skin irritation on the CD2027 9 µg/g ointment-treated side, including three (3) considered as severe by the investigators compared to 4 (10%) on the vehicle side (all considered as moderate). Five (5; 12.5%) subjects reported worsening of atopic dermatitis on the CD2027 9 µg/g ointment-treated side (none considered as severe) compared to four (4; 10%) on the vehicle-treated side (including one considered as severe).

Five (5) subjects experienced AE leading to discontinuation, considered as related for 4 of them. Three (3) subjects discontinued due to skin irritation on the CD2027 9 µg/g ointment-treated side and one subject discontinued for worsening of atopic dermatitis on the vehicle-treated side.

A total of 10 adverse events of special interest (AESIs) were reported by the Investigators. Four (4) of those were related to study treatment and led to the discontinuation of the subjects.

No subject died during the study, one subject had an unrelated serious adverse event reported (skull trauma).

Table 4 provides an overview of adverse events that occurred during this study.

Table 4 Overview of adverse events (Safety population)

MedDRA v11.0	CD2027 (N=40)		vehicle (N=40)		ALL (N=40)	
	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects
All AEs	46	25 (62.5%)	35	21 (52.5%)	54	26 (65.0%)
Related AEs	23	17 (42.5%)	11	7 (17.5%)	30	18 (45.0%)
All dermatologic AEs	26	20 (50.0%)	15	12 (30.0%)	34	22 (55.0%)
Related dermatologic AEs	21	17 (42.5%)	9	6 (15.0%)	28	18 (45.0%)
All serious AEs	1	1 (2.5%)	1	1 (2.5%)	1	1 (2.5%)
Related serious AEs	0	0	0	0	0	0
Severe AEs	7	4 (10.0%)	4	4 (10.0%)	8	5 (12.5%)
Related severe AEs	4	3 (7.5%)	1	1 (2.5%)	5	4 (10.0%)
AEs leading to discontinuation	4	4 (10.0%)	2	2 (5.0%)	5	5 (12.5%)
Related AEs leading to discontinuation	3	3 (7.5%)	1	1 (2.5%)	4	4 (10.0%)
AEs of Special interest	6	6 (15.0%)	5	5 (12.5%)	10	10 (25.0%)
Related AEs of Special interest	5	5 (12.5%)	3	3 (7.5%)	8	8 (20.0%)
Deaths	0	0	0	0	0	0

Adverse events are defined as events having occurred after the first use of medication
Each adverse event that was not reported on a specific side was summarized in each study treatment
Numbers in columns cannot be added because a given subject may have reported more than one AE.

Table 5 lists adverse events related to treatment with CD2027 9µg/g ointment or it's vehicle.

Table 5 Related adverse events (Safety population)

MedDRA v11.0	CD2027 (n=40)		vehicle (n=40)		ALL (n=40)	
	N events	N(%) Subj*	N events	N(%) Subj*	N events	N(%) Subj*
TOTAL NUMBER OF AEs	23	17 (42.5%)	11	7 (17.5%)	30	18 (45.0%)
Skin irritation	16	12 (30.0%)	5	4 (10.0%)	21	14 (35.0%)
Dermatitis atopic	5	5 (12.5%)	4	4 (10.0%)	7	6 (15.0%)
Blood 1,25-dihydroxycholecalciferol increased	1	1 (2.5%)	1	1 (2.5%)	1	1 (2.5%)
Lymphadenopathy	1	1 (2.5%)	1	1 (2.5%)	1	1 (2.5%)

Adverse events are defined as events occurred after the first use of medication
Each adverse event that was not reported on a specific side was summarized in each study treatment
Numbers in columns cannot be added because a given subject may have reported more than one AE.

Among the 30 related AEs, nine (9; 30%) were considered mild, sixteen (16; 53%) were considered as moderate and five (5; 17%) were considered as severe. Four of these 5 severe AEs were severe skin irritation on the CD2027 9 µg/g ointment side reported in 3 subjects and one was severe worsening of atopic dermatitis on the vehicle side of one subject.

In addition to the related AEs mentioned above, 3 severe AEs which were not considered as related to the treatments were reported: diarrhoea (one event in one subject), asthma (one event in one subject) and worsening of atopic dermatitis (one event in one subject). One serious adverse event (Skull Trauma), not related to the study product was reported, no death occurred during the study.

Five (5; 12.5%) subjects experienced an AE leading to discontinuation (Skin irritation or worsening of atopic dermatitis) from moderate (1 AE) to severe (4 AEs) intensity; 3 subjects discontinued due to skin irritation, that was considered related to study drug, on the CD2027 9 µg/g ointment-treated side and one subject discontinued for worsening of atopic dermatitis on the vehicle-treated side. The fifth subject experienced worsening of atopic dermatitis which was not side specific and was not considered related to any drug (Table 6).

Table 6 Adverse events leading to discontinuation (Safety population)

MedDRA v11.0		CD2027 (n=40)		vehicle (n=40)		ALL (n=40)	
		N events	N(%) Subj*	N events	N(%) Subj*	N events	N(%) Subj*
ANY ADVERSE EVENTS		4	4 (10.0%)	2	2 (5.0%)	5	5 (12.5%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		4	4 (10.0%)	2	2 (5.0%)	5	5 (12.5%)
	Skin irritation	3	3 (7.5%)	0	0	3	3 (7.5%)
	Atopic dermatitis	1	1 (2.5%)	2	2 (5.0%)	2	2 (5.0%)

Adverse events are defined as events occurred after the first use of medication
Each adverse event that was not reported on a specific side was summarized in each study treatment
A subject was counted once per preferred term even if more than one occurrence of the event was experienced
A subject was counted once per SOC even if more than one event was experienced within the SOC

At Day 29/Early Termination, no notable changes from screening were reported for hematology and blood chemistry parameters.

No subject had albumin-adjusted calcium levels shifted from ‘within’ to ‘above’ the upper limit of reference range from Baseline to Day 29/Early Termination.

Conclusion

CD2027 ointment 9 µg/g failed to show significant superiority to vehicle in the treatment of target lesions of Atopic Dermatitis. In addition, tolerance was low with a higher frequency of dermatological AEs related to CD2027 ointment compared to the vehicle.