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2. SYNOPSIS

NAME OF COMPANY: Galderma	***For regulatory use only***
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: NA	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT Number: 2008-002679-29 **IND Number:** 76064	
Study Title:	PLASMA PHARMACOKINETICS STUDY OF CD5024 1% CREAM IN SUBJECTS WITH PAPULOPUSTULAR ROSACEA

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2.1. Methodology

2.1.1. Study objective(s)

To investigate in maximal use conditions the pharmacokinetic profile of CD5024 1% cream applied once daily for four weeks in subjects with severe papulopustular *rosacea* (PPR).

2.1.2. Study design and clinical phase

Open-label, multicentre, single-treatment Phase 2 study investigating the PK profile of CD5024 1% cream applied once daily for four weeks on the face of subjects with severe PPR.

2.1.3. Study centre(s)

Five centres in France, Germany and Hungary.

2.1.4. Number of subjects

- Planned: 21 subjects;
- Treated: 17 subjects;
- Completed: 15 subjects.

2.1.5. Diagnosis and inclusion criteria

Male and female subjects, 18 years of age or older, with a diagnosis of PPR. Eligible subjects had to have an Investigator Global Assessment (IGA) score of 4 (severe) on a 5-point scale and present at least 25 inflammatory lesions on the face. Assessment (IGA) score of 4 (severe) on a 5-point scale and present at least 25 inflammatory lesions on the face.

2.1.6. Study period

From 29Aug 2008 (first subject enrolled) to 01Dec 2008 (last subject completed).

2.1.7. Investigational product

Table 1 Identity of Investigational Product

Trade Name or equivalent	Not applicable
Name of Drug Substance (INN)	Ivermectin
Internal code	CD5024
Pharmaceutical Form	Cream
Concentration	1%
Packaging	30 gram tube
Storage Conditions	Below 25°C (77°F)
Dosage (total daily dose)	1 gram
Dose regimen	
Route	Topical
Frequency	Once daily , between 7.00 and 10.00am
Duration of administration	4 weeks
Location of treated area	Face

2.1.8. Treatment duration and duration of subject participation

The study lasted approximately five months from time of initial subject enrolment to the completion of the last subject.

Prior to entering the active treatment phase, a screening period of up to 2 weeks was mandatory. Each subject was treated during a 4-week period and followed up for four-weeks. If necessary during this follow-up period, only topical treatment of *rosacea* using Metronidazole 0.75% cream (Rozex®, GALDERMA) twice daily was permitted. Metronidazole 0.75% cream tubes were provided by the Sponsor.

2.1.9. Evaluation criteria

2.1.9.1 Systemic Exposure

The pharmacokinetic analyses to assess the systemic exposure to CD5024 were conducted by GALDERMA R&D. Pharmacokinetic parameters were determined by a non-compartmental method from individual plasma concentrations.

The following pharmacokinetic parameters were determined as appropriate for each subject during the treatment period:

- C_{min} The pre dose plasma concentration of the drug at Days 1 (24 hours after 1st dose on D0), 7, 14, 21 and 28,
- C_{max} The observed peak drug concentration at Days 0,14 and 28;
- T_{max} The time at which C_{max} or Css_{max} occurs at Days 14 and 28;
- AUC_{0-24h} Area under the concentration-time curve at Days 0, 14 and 28.

Accumulation ratios were to be calculated according to the following formula:

- $R_1 = AUC_{(0-24h)}$ Day (14) / $AUC_{(0-24h)}$ Day (0);
- $R_2 = AUC_{(0-24h)}$ Day (28) / $AUC_{(0-24h)}$ Day (0);
- $R_3 = AUC_{(0-24h)}$ Day (28) / $AUC_{(0-24h)}$ Day (14).

When extrapolation was more than 20%, neither $AUC_{(0-inf)}$ nor $t_{1/2}$ was reported.

Mean values, standard error of mean (SEM) and the standard deviation (SD) were calculated and reported for each variable (Arithmetic mean for AUC, C_{max}, T_{max} and harmonic mean $t_{1/2}$).

2.1.9.2 Safety

- Any worsening of signs and symptoms of *rosacea*, such as stinging, burning, dryness, itching or erythema at D0 and D28 was recorded as an adverse event;
- Haematology and biochemistry blood tests at Screening and D28 visits;
- Adverse Events (AEs) at Baseline and at each following visit;
- Physical examination w at Screening, Day 28 and at Day 56/Early Termination;
- Vital signs (Blood pressure and heart rate) at Screening, D0, D28 and D56/Early Termination.

2.1.10. Disease assessment

- Investigator Global Assessment (IGA) Baseline and at each following visit ;
- Inflammatory lesions count Baseline and at each following visit.

2.1.11. Principal statistical methods

The following variables were summarised using descriptive statistics:

- Demographics and Baseline characteristics;
- Physical examinations and vital signs;
- Laboratory parameters;
- Inflammatory lesion counts, change and percent change from Baseline;
- IGA score and its change from Baseline;
- Plasma concentrations and pharmacokinetics parameters, when applicable;
- Adverse events.

The following specific analyses were performed on PK parameters:

C_{min} values on Day 1 (24 hours after 1st dose on D0), 7, 14, 21 and 28, and $AUC_{(0\text{-}24\ h)}$ on Day 0, Day 14 and Day 28 were transformed into natural logarithms (Ln). Each transformed parameter was submitted to an analysis of variance (ANOVA) including subject and time as factors in the model. The residual error variance was used to compute 90% confidence intervals.

2.2. Results

2.2.1. Subject disposition

A total of five investigators, one in France and two in both countries Germany and Hungary, screened 21 subjects; 17 received treatment.

From these 17 subjects, two discontinued the study prematurely; thus 15 subjects completed the study.

2.2.2. Demographics and Baseline data

The mean age of all 17 subjects was 54.3 ± 12 years (Min ~ Max: 35 / 74 years). The majority of subjects were females (11, 64.7%); all were Caucasian. The mean Baseline inflammatory lesion count was 40 ± 14.

Demographics are depicted in Table 2 below.

Table 2 Demographics (ITT population)

		Total
Age (in Years)	**N**	17
	Mean±SD	54.29±11.74
	Median	55.00
	Min~Max	35.00~74.00
Gender	**N**	17
	Female	11 (64.7%)
	Male	6 (35.3%)
Race	**N**	17
	Caucasian	17 (100.0%)

2.2.3. Pharmacokinetic results

After one single topical application of CD5024 1% cream, quantifiable CD5024 levels were detected in the plasma of all 17 subjects. A flat PK profile was observed over the dosing interval; plasma concentrations of CD5024 peaked within nine hours post dose (0.69 ng/mL range : 0.19 - 1.76 ng/mL) and then slowly decreased thereafter up to 0.37 ng/mL, 24 hours post-dose.

After 28 days of once daily topical application of CD5024 1 % cream, the systemic exposure was higher to that calculated after one single application. The arithmetic mean $AUC_{0\text{-}24\ H}$ were 9.29 ± 5.40, 36.14 ± 15.56 , 35.43 ± 14.42 ng.h/mL for Days 0, 14 and 28, respectively.

The statistical analysis of the $AUC_{0\text{-}24H}$ confirmed a time effect ($p<0.001$). Geometric means of $AUC_{0\text{-}24H}$ calculated at Days 14 and at 28 were at least four fold higher ($p<0.001$) than $AUC_{0\text{-}24H}$ calculated after one single application.

Similarly, after multiple topical applications, the C_{min} ratios (geometric mean) were at least 3-fold higher ($p<0.001$) at Days 7, 14, 21 and 28 compared to baseline (24 hours after one single application).

After 28 days of once daily topical application of CD5024 1 % cream, the arithmetic mean of systemic exposure over the dosing interval calculated at Day 14 ($AUC_{0\text{-}24H}$: 36.14 ± 15.56 ng.h/mL) and at Day 28 ($AUC_{0\text{-}24H}$: 35.43 ± 14.42 ng.h/mL) was similar, suggesting that that the steady state was reached. The same trend was observed with the pre-dose plasma concentrations (C_{min}). The arithmetic mean (± SD) pre-dose concentrations of CD5024 were 1.26 ± 0.53 ng/mL, 1.36 ± 0.66 ng/mL and 1.36 ± 0.63 ng/mL at Day 14, Day 21 and Day 28, respectively.

In addition, the statistical analysis demonstrated that there was no significant difference between the $AUC_{0\text{-}24H}$ calculated at Day 14 and Day 28 or between the C_{min} calculated at Days 7, 14, 21 and 28, thus confirming that the steady sate was reached at by Day 14.

Overall, the PK analysis showed that after the first topical administration, the CD5024 was not completely eliminated at the time of the second application and subsequently the CD5024 plasma concentrations were higher during the second dosing interval (superposition principle). After repeated topical application, plasma concentrations of CD5024 increased progressively until reaching a plateau (*i.e.* steady state condition). Statistical analysis demonstrated that the steady-state was already reached by Day 14 and at steady state, the accumulation ratio (evidenced by AUC and C_{min} ratios) was at least “3” versus a single application.

After the last application of CD5024 at Day 28, the apparent terminal half-life determined from 14 evaluable subjects was 145 hours (range: 92 - 238 hours); the last quantifiable concentration was observed approximately 24 days after application. In addition, the total systemic exposure at Day 28 ($AUC_{0\text{-}inf}$) was 312 ± 173 ng.h/mL. This prolonged apparent half-life indicates that CD5024 was slowly cleared from plasma after CD5024 treatment was stopped and was more prolonged than for an oral administration of CD5024. The $t_{1/2}$ for CD5024 orally administered is typically around 18 hours, ranging from about 12 to 20 hours. This terminal half-life after topical administration suggest that the rate limiting step in plasma CD5024 concentration decrease is the CD5024 disappearance from the administration site rather than the elimination rate.

Metabolism investigations were performed for three additional chromatographic peaks observed (M1, M2 and M3/M4). In addition, metabolism of CD5024 was also studied in several *in vitro* models: M1 was tentatively identified as 3''-O-desmethyl metabolite and M2 as monohydroxy metabolite (hydroxylation on the aglycone part).

Among these three metabolites, systemic exposure at steady state only to O-desmethyl CD5024 (M1) and mono hydroxyl CD5024 (M2) was more than 10 % of the parent drug.

The systemic exposure (arithmetic mean ± SD) of O-desmethyl CD5024 calculated at Day 14 ($AUC_{0\text{-}24H}$: 5.18 ± 3.76 ng.h/mL) and at Day 28 ($AUC_{0\text{-}24h}$: 4.25 ± 3.21 ng.h/mL) were similar, indicating that steady-state was already reached by Day 14. The same tendency was observed with the monohydroxy CD5024, with similar systemic exposures at Day 14 and Day 28 (Day 14: $AUC_{0\text{-}24H}$: 4.21 ± 2.12 ng.h/mL, Day 28: $AUC_{0\text{-}24h}$: 4.08 ± 1.83 ng.h/mL).

At the end of the 28-day application period, all metabolites had slowly cleared from the plasma, the last quantifiable concentration being observed four to eight days after the last application. This plasma decrease was faster than the one observed for the parent drug and subsequently, when considering the total quantifiable systemic exposure at steady state ($AUC_{0\text{-}t}$); all metabolites were formed at lower than 10 % of parent drug systemic exposure.

Table 3 Overview of pharmacokinetic results

		Baseline	Day 7	Day 14	Day 21	Day 28
C_{min} (ng /mL)	N	17	13	14	14	15
	Geometric Mean	0.33	0.98	1.16	1.25	1.24
	Arithmetic Mean ± SD	0.37 ± 0.21	1.17 ± 0.88	1.26 ± 0.53	1.36 ± 0.66	1.36 ± 0.63
	Min~Max	0.17~0.86	0.56~3.26	0.58~2.34	0.66~3.25	0.53~3.00
AUC_{0-24h} (ng.h/mL)	N	15	-	15	-	15
	Geometric Mean	33.21	-	33.21	-	32.72
	Arithmetic Mean ± SD	36.14 ± 15.56	-	36.14 ± 15.56	-	35.43 ± 14.42
	Min~Max	13.69~75.16	-	13.69~75.16	-	12.89~70.08
C_{max} (ng/mL)	N	17	-	15	-	15
	Geometric Mean	0.54	-	1.85	-	1.58
	Arithmetic Mean ± SD	0.69 ± 0.49		2.10 ± 1.04	-	1.74 ± 0.77
	Min~Max	0.19~1.76		0.69~4.02	-	0.58~3.36
AUC_{0-t} (ng.h/mL)	N	-	-	-	-	15
	Geometric Mean	-	-	-	-	232.85
	Arithmetic Mean ± SD	-	-	-	-	274.62 ± 159.31
	Min~Max	-	-	-	-	63.87~655.28
AUC_{0-inf} (ng.h/mL)	N	-	-	-	-	14
	Geometric Mean	-	-	-	-	273.50
	Arithmetic Mean ± SD	-	-	-	-	311.74 ± 173.20
	Min~Max	-	-	-	-	115.67~718.89
Terminal Half Life (h)	N	-	-	-	-	14
	Harmonic Mean	-	-	-	-	145
	Min~Max	-	-	-	-	92:00~238

2.2.4. Safety

None of the six events reported during the study was considered by the investigators as related to CD5024, or as severe. None of the events led to study discontinuation of the subjects. No deaths, other serious adverse events and certain other significant adverse events were reported during the course of the study.

Results for haematology, blood chemistry and urine parameters after 28 days of treatment with CD5024 showed no relevant changes from Screening.

Descriptive results for *rosacea* signs and symptoms (dryness, erythema, itching and singing/burning) scores showed a decrease of severity for all parameters after 28 days of treatment.

Results at Screening, Baseline, Day 28 and Day 56 for vital signs and physical findings did not raise safety concerns.

2.2.5. Disease assessment

After 28 days of treatment with CD5024 1% cream, the mean number of inflammatory lesions in 16 subjects had decreased from 40.47 ± 14.31 to 20.56 ± 14.90. The mean percent change from Baseline was -52.38 ± 27.72.

Descriptive results of the investigator global assessment (IGA) in 16 subjects showed that after 28 days of treatment two (2, 12.5%) subjects from the initial 17 subjects still presented with a severe *rosacea* whereas 14 (87.5%) subjects improved from Baseline by at least one grade. The majority of subjects (9, 5.6%) had a moderate *rosacea*.

2.3. Conclusion

The present study was conducted under maximal study conditions (1 gram of CD5024 1 % cream once daily applied on the face under controlled conditions) in subjects towards upper level of severity (IGA score of 4 with 40.47 ± 14.31 facial lesions*)*.

A total of 21 subjects, with a majority of females were enrolled; 17 received treatment and 15 completed the study. The mean age of subjects was 54.9 years. Multiple PK plasma samples were obtained at several time periods during the 28-day treatment and after the last application in order to capture the complete PK profile of CD5024 (and its metabolites) over time.

After repeated topical application of CD5024 1% cream, systemic exposure to CD5024 increased with the number of topical application until reaching a plateau (steady state condition). Under the experimental conditions described herewith, the statistical analysis demonstrated that the steady-state was reached at Day 14 with an accumulation ratio of at least “3”, using AUCs and C_{min} ratios.

The slow, but constant release of CD5024 from the skin into the blood (evidenced by long terminal half-lives) at the end of treatment indicated a CD5024 reservoir in the skin. These prolonged terminal half-lives after topical administration suggest that the rate limiting step in plasma CD5024 concentration decrease is the CD5024 disappearance from the administration site rather than the elimination rate itself (flip flop phenomenon). Despite this rate-limiting factor, the statistical analysis suggested that no further systemic accumulation of CD5024 was expected in a prolonged treatment with CD5024 1 % cream, applied once daily in subjects with severe papulopustular *rosacea.*

In addition, among the three metabolites detected in plasma samples, only O-desmethyl CD5024 and mono hydroxyl CD5024 were formed at greater than 10 % of parent drug systemic exposure at steady state. At the end of the application period, all metabolites were slowly cleared from the plasma, this decrease was faster than the one observed for CD5024.

The steady state was reached by 14 for all metabolites and no further systemic accumulation of was expected in a longer treatment duration.

Topical treatment with CD5024 1% cream once daily over four weeks was well tolerated and resulted in a noteworthy decrease in inflammatory lesions and in a high percentage of subjects with improved papulopustular *rosacea*.