Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY: GALDERMA R&D	***For regulatory use only***	
NAME OF FINISHED MEDICINAL PRODUCT: CD5024 1% CREAM		
NAME OF ACTIVE INGREDIENT(S): CD5024		
Title of study:	A MULTICENTER, OPEN-LABEL STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF CD5024 1% CREAM TREATMENT FOR UP TO 52 WEEKS IN SUBJECTS WITH PAPULO-PUSTULAR ROSACEA	

METHODOLOGY

Study objective(s):
To document the long-term safety of CD5024 1% cream once daily, for up to 52 weeks of topical treatment in subjects with Papulo-Pustular Rosacea in accordance with the ICH E1A guidance.

Additionally to evaluate the long-term efficacy of CD5024 1% cream under these conditions.

These objectives were changed to an evaluation for up to subject's termination as a result of the Sponsor's decision to discontinue the study prematurely as detailed below (see Study period).

Study design and clinical phase:
Phase 3 therapeutic confirmatory, 52-week multicenter, open-label Long-Term Safety study.

Study center(s):
52 sites in Europe (France, Germany, Czech Republic, Hungary, Bulgaria, Romania, and Iceland) and Australia

Number of subjects:
Planned: 450 subjects
Randomized: Not Applicable
Eligible: 484 subjects

Diagnosis and Inclusion criteria:
Male and female subjects, 18 years of age or older, with a diagnosis of Papulo-Pustular Rosacea, presenting with 15 to 70 inflammatory lesions, and having an Investigator's Global Assessment (IGA) score of rosacea of 3 (moderate) or 4 (severe) on a 5-point scale

Study period:
From 27 August 2008 (first subject enrolled) to 17 April 2009 (last subject completed).

The study was stopped prematurely due to abnormal laboratory findings observed in some patients: at Week 10 of treatment, the neutrophil cell count (NCC, a predefined test in the study) had decreased in 3 subjects below the threshold value of 1.5 Gcell/L defining a neutropenia. Neither concomitant treatment nor concomitant pathology could be attributed to this decrease in the neutrophil count. The mild to moderate neutropenia observed in these 3 subjects was not associated to any clinical signs or symptom.

The study was halted on 16 January 2009 and all study subjects were required to immediately stop treatment; the protocol was amended on 28 January 2009 to include a one-month safety follow up after treatment discontinuation. The decision to discontinue the study was taken on 17 February 2009 and was motivated by the following considerations, related to the study specificity and outcomes:

- The study was not conceived to implement a close subject follow-up.
- The measures put in place after the first observations (implementation of a Decision Tree on neutropenia and follow-up providing for specific guidance on NCC monitoring and treatment continuation) were difficult to implement because the majority of subjects could not visit the study centers every 48 hours.
- The existence of a potential neutropenia-inducing factor of unknown nature occurring in the study could not be ruled out.

Due to this change, the initial objective of evaluating the long-term safety of CD5024 1% cream once daily in the topical treatment of Papulo-Pustular Rosacea for up to 52 weeks was changed to an evaluation for up to subject's termination. In the following, two periods of the study are considered for each subject:

- From first use to last use of the product: the 'Treatment period'.
- After last use of the product: the 'Safety Follow-up period' as per protocol amendment.

Investigational products:

Test Product Dosage Form:	**CD5024 1% cream**		
Dosage regimen:	**Once daily**		
Route of administration:	Topical application on the whole face		
Batch/formulation number	575.754/056256		
Treatment duration	Initial protocol: up to 52 weeks Actual treatment duration: Mean duration = 84.3 days (from 4 days to 196 days) Actual safety follow-up duration: Mean duration = 32.8 days		

Criteria for evaluation:

- **Efficacy**

Efficacy evaluation was initially planned at Baseline, Week 4, then every 6 weeks up to Week 52/Early Termination visits, and unscheduled visits. This evaluation could actually be performed up to Week 22 of treatment in some subjects. A global evaluation of improvement from Baseline was made considering the last value available for each subject (as detailed in **Summary Table 3**). Efficacy criteria were:

- Investigator's Global Assessment (IGA) of rosacea using a 0 (clear) to 4 (severe) grading scale.
- Inflammatory lesion counts (papules, pustules).
- Erythema assessment using a 0 (no erythema) to 4 (fiery red) grading scale.

- **Safety**

Safety assessment planned in the initial protocol consisted in adverse event recording, medical monitoring / physical examination and blood sampling. This was converted to a one-month safety follow up after treatment discontinuation as defined in the amended protocol: in addition to the above assessments, a specific safety follow-up was to be implemented in the presence of clinical signs of infection, in the presence of fever with or without signs of infection, or if the total NCC was below the threshold value of 1.5 Gcell/L at the first blood sampling performed after treatment discontinuation. Thus:

- Adverse events were recorded at each study visit of the Treatment and Safety Follow-up periods.
- Physical examination and vital signs evaluation were initially planned at Screening, Week 10, Week 28, Week 40, Week 52/Early termination visits and unscheduled visits, if deemed necessary by the investigator. These evaluations were actually performed at Week 10 of treatment and at each visit of the Safety Follow-up period. The specific, additional safety follow-up defined above included pulmonary X-ray, aerobic and anaerobic hemocultures, urinary cultures and various serologies.
- Laboratory safety tests (blood chemistry, hematology): in the initial protocol blood samples were to be obtained at Screening visit (results to be available for Baseline visit), Week 10, Week 28, Week 40, Week 52/Early Termination Visit and unscheduled visits, if deemed necessary by the investigator. During the Treatment period, these laboratory tests were actually performed up to Week 16 of treatment with most of the results coming from Week 10 samples. During the Follow-up period:

- Hematology tests were performed at first visit after treatment discontinuation. If the NCC at this visit was ≥ 1.5 Gcell/L, then hematology tests were to be performed every 15 days during 1 month after treatment discontinuation. In the case of the specific, additional safety follow-up defined above (signs of infection, fever, or NCC<1.5 Gcell/L), blood samplings for hematology were to be performed every 48 hours until disappearance of the signs or until NCC was above 1.5 Gcell/L in two consecutive samplings. Then hematology tests were to be performed every 15 days up to 1 month after treatment discontinuation.
- Blood chemistry tests were to be performed (1) if abnormal biochemistry values, judged as clinically significant, were observed at sampling of the Week 10 treatment visit, or (2) when the Safety Follow-up was started prior to this Week 10 laboratory assessment.

- Signs and symptoms of rosacea: evaluation of the outcome of Stinging/Burning, Dryness, and Itching on a 4-point scale were to be performed at each study visit.

- **Systemic Exposure**
  - Determination of plasma levels of CD5024 was initially scheduled on a subset of 70 subjects at Week 10, Week 28 and Week 52/EarlyTermination visits. This pharmacokinetic (PK) analysis was actually performed for 79 subjects at their Week 10 treatment visit. During the Safety Follow-up, PK blood sampling was to be carried out at least on each subject presenting abnormalities in biological parameters at the first blood sampling after treatment discontinuation, then every 15 days up to 1 month after treatment discontinuation.

- **Other Assessments**
  - Subject's completion of a validated dermatologic Quality of Life questionnaire (Dermatology Life Quality Index DLQI™) was initially planned At Baseline, Week 16, Week 34 and Week 52/Early Termination visits. Due to study interruption, DLQI™ questionnaires were completed only at Baseline and up to Week 16/final visit.
  - The following assessments were initially to be made at Week 16, Week 34 and Week 52/Early Termination visits:
    - Subject's assessment of his/her rosacea compared to Baseline using a 1 (excellent improvement) to 5 (worse) scale. This assessment was actually performed at Baseline and final visit.
    - Subject's Appreciation Questionnaire (specific self-administered questionnaire) to document subject's satisfaction with the product and its use. This assessment was actually performed at final visit.

Principal statistical methods:

Descriptive statistics were used to summarize the data. No formal statistical hypotheses were to be tested.

- **Efficacy**

All efficacy variables were analyzed based on the Intention To Treat (ITT)-Observed Cases population and also on the ITT-Last Value Available for longitudinal data.

Efficacy variables were descriptively summarized at each visit. The categorical variables (IGA, erythema score) and their changes from Baseline were summarized by frequency and percentage for each response category (N, %). The continuous variables (lesion counts, changes or percent changes) were summarized using means, medians, Q1, Q3, minimum, maximum, and standard deviations for the data collected at each visit. Analyses of time to event were planned in the initial protocol but were abandoned due to study discontinuation.

- **Safety**

All safety data were summarized based on the safety population. Due to study discontinuation, analyses of the safety parameters (Adverse events and Laboratory values) were broken down in the two periods: Treatment period and Follow-up period. Moreover during the Safety Follow-up period the analysis of blood parameters was summarized according to the status in neutrophil counts (<1.5 G/L or ≥1.5 G/L) obtained before the end of the Treatment period.

- Adverse Events were tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary.
- Evaluation of clinical laboratory test results were made through shift tables based on normal ranges from Screening (1) up to the end of the Treatment period and (2) up to the end of the Follow-up period.
- Vital signs and physical examinations were descriptively summarized.
- Signs and symptoms were descriptively summarized using standard statistics (N, mean, SD, Min and Max values or frequency tables) and also worst response over post-treatment visits. They were also categorized as (1) no worsening from baseline, (2) worsening from baseline and maximum severity reached.
- Exploratory analyses on neutrophil cell counts were performed. These analyses consisted in focusing on the percent change from Baseline and the categorization of that change. Neutrophil percent change from Baseline was categorized into decrease or increase/no change. Neutrophil counts (change from Baseline and/or percent change from Baseline) were plotted against percent change from Baseline in lesion counts at final value under treatment, white blood cell count, lymphocyte count, monocyte count, CD5024 plasma concentration (C_{ss}) and quantity of product used.

- **Systemic Exposure and Other Analyses**
  - Descriptive statistics on CD5024 plasma concentration at steady-state (C_{ss}) including N, mean, SD, Min and Max values), initially planned to be summarized at each sampling period (Week 10, Week 28, Week 52) from the original raw data and after natural log (Ln) transformation of the data, were actually summarized during the Treatment period and the Safety Follow-up. C_{ss} was described by visit and no ratios were calculated.
  - Quality of life and subject's appreciation and subject's assessment questionnaires were descriptively summarized using standard statistics (N, mean, SD, Min and Max values or frequency tables).

RESULTS

- **Subject Disposition**

A total of 484 subjects were included and received study treatment. Both the ITT population and the safety population consisted of all 484 subjects. No per protocol efficacy analysis was planned for this non-comparative safety study.

After treatment discontinuation per Sponsor's request, a total of 477 subjects entered the Safety Follow-up.

Summary Table 1a Subject Disposition - Overall

	Treatment Period	Safety Follow-up Period	Overall
ITT/Safety population N	484	477	484
Discontinued N (%)	7 (1.4%)	477 (100%)	484 (100%)
Adverse event	1 (0.2%)	6 (1.3%)	7 (1.4%)
Subject's request	4 (0.8%)	102 (21.4%)	106 (21.9%)
Protocol violation	-	2 (0.4%)	2 (0.4%)
Lost to Follow-up	1 (0.2%)	4 (0.8%)	5 (1.0%)
Other reasons	1 (0.2%)	363 (76.1%)[a]	364 (75.2%)

a. These 363 subjects were submitted to the entire Safety Follow-up

Summary Table 1b Subject Disposition - Assessments - Treatment Period (N=484)

N Subjects	Investigator's Assessment				Blood Analysis		
	Efficacy & Safety	Signs and Symptoms	Vital Signs	Physical Examination	Blood Chemistry	Hematology	PK
Baseline	484	484	-	-	-	1[a]	-
Week 4	474	474	-	-	1[b]	1[b]	-
Week 10	334	334	325	326	324	306	79
Week 16	40	40	-	-	4[c]	11[d]	-
Week 22	2	2	-	-	-		-

[a]. This subject had haematology determination at Day 7 only; [b]. No other blood sampling was performed during treatment of this subject

[c]. All these 4 subjects had also blood chemistry determination at Week 10; [d]. 10 of these 11 subjects also had hematology determination at Week 10

Summary Table 1c Subject Disposition - Assessments - Safety Follow-up Period (N=477)

N Subjects	Investigator's Assessment	Blood Analysis			
	Safety Follow-up - Vital Signs Physical Examination - Signs and Symptoms	Blood Chemistry	Hematology Follow-up		PK
			Regular	Specific[a]	
	477	316	460	0	6

a. Additional hematology follow-up as described above in: Methodology / Criteria for evaluation / Safety

■ Demographics and Baseline Data

Demographics and Baseline disease characteristics (IGA score, inflammatory lesions) are depicted in Summary Table 2 below:

		Total
	N (%)	484
Gender n (%)	Female	333 (68.8%)
	Male	151 (31.2%)
Race n (%)	Caucasian	479 (99.0%)
	Hispanic	2 (0.4%)
	Asian	1 (0.2%)
	Other	2 (0.4%)
Age (years)	<65 Years	420 (86.8%)
	≥65 Years	64 (13.2%)
	Mean±SD	50.8±12.4
IGA score[a]	3	399 (82.4%)
	4	85 (17.6%)
Inflammatory lesion counts	Mean±SD	31.9±12.4
	Median	28.0
	Min~Max	15~70

a. 0: Clear; 1: Almost clear; 2: Mild; 3: Moderate; 4: Severe

■ Efficacy

Summary Table 3 IGA score, inflammatory lesion counts, erythema score: change from Baseline to last value available (N=484)

Distribution of change of IGA score	N (%)		Inflammatory lesion counts	Erythema scores
-4	1 (0.2%)	Baseline: Mean ± SD	31.9±12.4	2.5±0.7
-3	22 (4.5%)	Baseline: Median	28.0	3.0
-2	135 (27.9%)	Baseline: Min~Max	15~70	0~4
-1	221 (45.7%)	Change: Mean ± SD	-19.2±13.8	-0.8±0.9
0	100 (20.7%)	Change: Median	-17.0	-1.0
1	5 (1.0%)	Change: Min~Max	-63~23	-3~1

This study was not designed (open label) to draw any conclusions on the efficacy of the product. However it is observed that during the study the majority of patients treated showed an improvement of their symptoms. Subject questionnaires confirmed this trend.

- **Safety**

Overview of adverse events

A total of 248 events were recorded during the Treatment period in 172 subjects out of 484 (35.5%); 73 events were recorded during the Follow-up period in 58 subjects out of 477 (as detailed in **Summary Table 4**). One subject (0.2%) experienced a non-treatment related serious adverse event during the Screening period (i.e. prior to receiving study treatment), 5 subjects (1.0%) during their Treatment period, and 1 subject (0.2%) during the Follow-up period. A total of 7 subjects discontinued the study due to adverse events, including 3 related to treatment (see below). There were no deaths and no pregnancies reported during the study.

Related adverse events (26 events) were recorded in 20 subjects (4.1%) during their Treatment period, but none was recorded during the Follow-up. Of these 26 events, 5 led to discontinuation in 3 subjects (0.6%):

- One subject had mild skin irritation.
- One subject had mild skin discomfort.
- One subject had severe gastrooesophageal reflux disease, moderate headache and severe pustular rash on the nose. This subject had previously experienced 2 AEs, mild clonus and severe paraesthesia, which had also been considered related to treatment. Of note, the investigator specified that these events had all been reported by the subject, and that he was unable to confirm them.

Related adverse events were mostly cutaneous events (18 of the 26 related AEs). These related cutaneous AEs were often mild in intensity and represented mostly an irritant reaction to the medication. Aggravation of rosacea was seen in 3 subjects during treatment. These events occurred during the first month of treatment in most instances and all resolved spontaneously.

Summary Table 4 Overview of Adverse Events (Safety population)

	TREATMENT PERIOD (N=484)		FOLLOW-UP PERIOD (N=477)		OVERALL (N=484)	
	n events	n (%) subjects	n events	n (%) subjects	n events	n (%) subjects
All AEs	248	172 (35.5%)	73	58 (12.2%)	321	202 (41.7%)
Related AEs	26	20 (4.1%)	0	0	26	20 (4.1%)
All dermatologic AEs	35	31 (6.4%)	4	3 (0.6%)	39	34 (7.0%)
Related dermatologic AEs	18	17 (3.5%)	0	0	18	17 (3.5%)
All serious AEs	5	5 (1.0%)	1	1 (0.2%)	6	6 (1.2%)
Related serious AEs	0	0	0	0	0	0
Severe AEs	10	8 (1.7%)	1	1 (0.2%)	11	9 (1.9%)
Related severe AEs	4	2 (0.4%)	0	0	4	2 (0.4%)
AEs leading to discontinuation	9	7 (1.4%)	1	1 (0.2%)	10	7 (1.4%)
Related AEs leading to discontinuation	5	3 (0.6%)	0	0	5	3 (0.6%)
Deaths	0	0	0	0	0	0

Other related AEs (8 of 26) were under the following categories:

- Eye disorders: 1 event.
- Nervous system disorders: 4 events.
- Gastrointestinal disorders: 1 event.
- Infections and infestations: 1 event.
- Blood and lymphatic system disorders: 1 event.

The latter was a moderate neutropenia observed in a subject (Subject No 2803) after 77 days of treatment. This specific question is addressed in detail in section **Clinical laboratory evaluation** below. The 2 cases of mild neutropenia observed at Week 10 of treatment were not reported as adverse events (Subjects No 1919 and 5138).

Cutaneous tolerance, vital signs, physical findings, and other observations related to safety
Globally, Stinging/Burning, Itching and Dryness scores (mean and median values) were lower compared to Baseline as early as at Week 4 visit.

Vital signs measured in the 484 subjects enrolled at Screening, were then measured in 325 subjects at their Week 10 visit, and 328 subjects at their last visit under treatment. Vital signs were also recorded in 450 subjects at the end of the Safety Follow-up period. No clinically notable change was observed throughout the study.

Physical examination (with body system evaluated as “normal” or “abnormal” by the investigator) was performed at their Week 10 visit in 326 subjects out the 484 subjects enrolled at Screening. The investigators examined 332 subjects at their last visit under treatment and 468 subjects at the end of the Safety Follow-up visits. There were no major findings throughout the study.

Clinical laboratory evaluation

The two periods of the study were considered: the Treatment period which for the specific sake of the analysis of laboratory parameters starts from subject enrolment (i.e. pre-treatment laboratory values obtained prior to first use) and goes until last use of treatment, and the Follow-up period (after last use of treatment). There was a particular focus on the neutrophil count status of the subjects. Thus, laboratory parameters of the Follow-up period were summarized depending on the neutrophil count status observed until last use of the product (1) for subjects having NCC≥1.5 Gcell/L, (2) for subjects having NCC<1.5 Gcell/L. Five subjects presented with NCC values <1.5 Gcell/L during the study period, 2 of them prior to first treatment use (Subjects No 3006: NCC=1.44 Gcell/L, and 2111: NCC=1.15 Gcell/L), and 3 of them during treatment (the 3 subjects with some degree of neutropenia at Week 10 of treatment: Subjects No 1919: NCC=1.06 Gcell/L, 5138: NCC=1.23 Gcell/L, and 2803: NCC=0.79 Gcell/L).

Blood Chemistry

- Blood chemistry data available at the end of the Treatment period for 325 subjects did not show any clinically significant change from Baseline in any of the blood chemistry parameters.
- Blood chemistry data were available from 316 subjects out of 477 at the end of the Follow-up period. Out of these 316 subjects, 179 (excluding the 5 subjects with NCC values <1.5 Gcell/L during their Treatment period) had paired data End of follow-up versus End of treatment showing no clinically significant change in any of the blood chemistry parameters.
- Blood chemistry parameters in the 5 subjects with NCC<1.5 Gcell/L during the Treatment period were mostly within reference values of the central laboratory throughout the study (Treatment and Follow-up periods). A limited number (13) of out-of-reference values were reported. None of these values were considered clinically significant.

Hematology

- Global analysis of the hematology data available for 309 subjects at the end of the Treatment period compared to Baseline (shift tables) did not raise any particular signal with respect to any of the hematology parameters including neutrophil and white blood cell counts.
- Hematology data were available from 460 subjects out of 477 at the end of the Follow-up period. Out of these 460 subjects, 296 (excluding the 5 subjects with NCC values <1.5 Gcell/L during their Treatment period) had paired data End of follow-up versus End of treatment showing no clinically significant change in any of the hematology parameters.

- Hematology parameters in the 5 subjects with NCC<1.5 Gcell/L during the Treatment period were recorded throughout the study (Treatment and Follow-up periods). None of the out-of-reference values in these subjects were considered clinically significant, with the exception of the neutropenia (NCC=0.79 Gcell/L) observed in Subject No 2803 at Week 10 of treatment. All these subjects had reverted to NCC values above the neutropenia threshold (NCC≥1.5 Gcell/L), either while still under treatment (Subjects No 3006, 1919 and 2111) or during the Safety Follow-up period (Subjects No 5138 and 2803).

Exploratory analyses on neutrophils

- **Categorization of the percent change from Baseline in neutrophil counts under treatment**: neutrophil count variations observed during treatment were categorized in terms of decrease or increase from Baseline. This analysis, when performed for neutrophil counts measured up to the End of treatment, shows that of the 305 subjects under treatment with hematology results at last sampling before last use:
  - 184 (60.3%) had a decrease of neutrophil count. In these 184 subjects, the median decrease was 19.0% from Baseline. A decrease of more than 30% (i.e. NCC lower than Baseline x 0.7) was observed in 54 subjects (17.8% of the 305 subjects).
  - 121 (39.7%) had an increase of neutrophil count. In these 121 subjects, the median increase was 19.4% from Baseline. An increase of more than 42.9% (i.e. NCC higher than Baseline / 0.7) was observed in 24 subjects (7.8% of the 305 subjects).
  - The global change from Baseline in the 305 subjects was a decrease of neutrophil count (median change) of 6.9%.
- **Change in neutrophil counts in relation to plasma concentrations of CD5024**: A possible relationship between neutrophil counts and exposure to CD5024 was explored using the data obtained for both parameters at the same blood sampling after Baseline (i.e. both Treatment and Follow-up periods were considered). In this analysis, BLQ values were imputed to the lower limit of quantification, 0.05 ng/mL. There was no correlation between individual CD5024 plasma concentrations and individual neutrophil counts measured at the same sampling. In particular:
  - In 4 subjects with neutrophil counts below the central laboratory normal range of 1.8 Gcell/L, exposure to CD5024 was either below or just above the quantification limit. Three of these subjects were part of the 5 subjects with NCC<1.5 Gcell/L discussed previously: Subjects No 3006, 1919 and 2111.
  - The highest CD5024 plasma concentrations were measured in 4 subjects at Day 71 of treatment (from 2.94 ng/mL to 5.48 ng/mL), all with neutrophil counts within the central laboratory normal range.
- **Other exploratory analyses**: there was no relation between change in neutrophil counts at the end of the Treatment period and:
  - Treatment efficacy (as assessed with IGA scores and inflammatory lesion counts).
  - Quantity of product used.
  - White blood cell counts, lymphocyte counts and monocyte counts at the end of the Treatment period.

- **Systemic Exposure**

During the treatment period, a total of 81 plasma samples were collected from 80 subjects (79 samples were analyzed). The total treatment duration ranged from 9.5 to 10.5 weeks. The mean (± SD) plasma concentration of CD5024 was 0.898±0.901 ng/mL (range: <0.05 ng/mL to 5.48 ng/mL). Exposure data obtained in this study were in agreement with the PK profile of CD5024 1 % cream previously established in subjects with Papulo-Pustular Rosacea. There was no correlation between CD5024 plasma concentrations and the treatment effect.

PK analysis performed during the Follow-up period in 6 subjects showed that plasma concentrations of CD5024 were below the limit of quantification for 4 subjects, and varied from 0.0542 ng/mL to 0.3727 ng/mL in the other 2 subjects.

- Other Assessments

Not applicable

CONCLUSION

No serious treatment related adverse event was observed during the study. Non serious treatment related adverse events (26 events) were recorded in 20 subjects during the Treatment period, but none was recorded during the Follow-up period. Related adverse events were mostly cutaneous events which resolved spontaneously.

Neutropenia was the only remarkable safety observation of the study:

- Three events of neutropenia with cell counts below 1.5 G/L were observed under treatment. One event - a count of 0.79 Gcell/L - was close to the threshold of 0.50 Gcell/L where life threatening complications can occur.
- No serious infection was reported and neutropenia was reversible in the three subjects even under treatment for one of them.
- No cause of neutropenia was identified in past medical history, concurrent diseases or concomitant treatments of the 3 subjects with neutropenia.
- Neutrophil cell counts decreased by 6.9% (median at End of treatment) in the study:
- -60.3% of the subjects experienced a decrease in neutrophil counts from screening to End of treatment.
- -17.8% of the subjects experienced a decrease of more than 30% of their neutrophil counts from screening to End of treatment.
- Conversely, 39.8% of the subjects experienced some increase in neutrophil counts and 7.1% of the subjects experienced an increase of more than 42.9% of their neutrophil counts, from Screening to Week 10 of treatment.

- The study population - demographics, disease severity and plasma drug levels - was comparable to the previous studies conducted with CD5024 cream.
- No correlation between CD5024 plasma concentration and individual neutrophil counts could be established.
- No correlation between treatment efficacy and neutrophil counts could be established.

Moreover, the incidence of neutropenia observed in this study was comparable to that observed in the general Caucasian population (~ 1% in this study vs. 0.5% in the general population). In addition, NCC variations reported in this study were within the rate of physiological variability in a normal population. These observations suggest that the neutropenia events observed in this study remain compatible with the hypothesis of a random occurrence, in the absence of a drug relationship. However the design of this LTS study, without a control group, is not appropriate to investigate this hypothesis. Therefore a drug relationship cannot be firmly ruled out at this stage.