Clinical Study Synopsis for Public Disclosure

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2. SYNOPSIS

NAME OF COMPANY:	***For regulatory use only***
Galderma	
NAME OF FINISHED MEDICINAL PRODUCT:	
CD5024 1% Cream	
NAME OF ACTIVE INGREDIENT(S):	
Ivermectin	
Title of study:	A Double-Blind, Vehicle-Controlled, Parallel-Group Study Assessing the Activity of CD5024 1% Cream in Subjects with Papulopustular Rosacea over 12 Weeks Treatment

- **Study centres**

Twenty-four (24) study centres in 6 countries (France, Germany, Czech Republic, Hungary, Finland, and Slovakia) participated in this study.

- **Clinical phase**

Phase 2

- **Study period**
  - Date of first screened: 28 Sep 2010
  - Date of last subject completed: 02 May 2011

- **Study objectives**

- Safety objectives
  - The primary objective of this Phase 2 study was to investigate a potential effect of CD5024 on the induction of neutropenia in subjects with Papulopustular Rosacea (PPR) in comparison to its vehicle. Haematological safety was to be ensured by close following by an Independent Data Monitoring Committee (IDMC).
  - Secondary objectives were to assess the general safety of CD5024, and its efficacy versus vehicle.
- Co-primary efficacy objectives
  - To assess CD5024 cream versus vehicle in terms of improvement in Investigator Global Assessment score from Baseline
  - To assess CD5024 cream versus vehicle in terms of absolute change in inflammatory lesion count from Baseline.

- Other objectives
  - Analyses of systemic exposure to CD5024 at each visit during treatment and for individual cases of NCCs less than 1.5 G/L were to be performed.

- **Study design**

- A multicentre, prospective, double-blind, randomized, vehicle-controlled, parallel group study conducted in subjects with PPR over 12 weeks of treatment with once daily application of CD5024 cream 1% or its vehicle.

- **Total number of subjects**

In total, 304 subjects were screened and 210 subjects were randomised from 24 centres in 6 countries to receive CD5024 1% (N = 104) or CD5024 Vehicle (N = 106). Of these, 210 subjects comprised the Safety and Intent-to-Treat (ITT) populations and 186 (88.6%) subjects were included in the Per-Protocol (PP) population.

- **Diagnosis and key inclusion and non-inclusion criteria**
  - Key inclusion criteria

  Male and female subjects, 18 years of age or older, with a diagnosis of PPR. Eligible subjects must have presented with at least 15 inflammatory lesions, and have had an Investigator Global Assessment (IGA) score of 3 (moderate) or 4 (severe) on a 5-point scale

  - Key non-inclusion criteria

  Subjects with particular forms of rosacea that could be confounded with PPR, subjects with ocular rosacea requiring systemic or an interfering treatment, subjects with underlying diseases putting them at risk, or subjects with clinically significant neutrophil cell count (NCC) abnormalities.

- **Test product dosage form**

	Investigational Product	Comparator
Trade Name or equivalent	Not applicable	Not applicable
Name of Drug Substance (INN)	Ivermectin	Not applicable
Internal code	CD5024	CD5024 vehicle
Pharmaceutical Form	cream	cream
Concentration	1%	0%
Packaging (type and size)	30 g tube	30 g tube
Storage Conditions	Below 25°C (77°C)	Below 25°C (77°C)
Dosage (total daily dose)	one pea-size amount to each of 5 facial regions	one pea-size amount to each of 5 facial regions
Dose regimen		
Route	Topical	Topical
Frequency	Once daily	Once daily
Duration of administration	12 weeks	12 weeks
Location of treated area	face	face

- **Safety assessment:**
  - Haematological assessments:

    NCC assessed every 2 weeks during the month prior to Baseline, every 2 weeks during the 12-week treatment period, and one month after study treatment discontinuation

  - Biochemistry assessments:

    Biochemistry assessed at Screening and at Baseline, followed by every 4 weeks and in case of retest

  - Serologies

    Antimicrobial serologies performed in case of neutropenia (≤1.5 GigaCells/L)

  - Physical examination

    Physical examination, including vital signs, performed at Screening, Baseline, and 4, 8, 12, and 16 weeks after treatment commencement, as well as unscheduled visits. Vital signs recorded at every other visit.

  - Adverse events (AEs)

    AEs reported at every visit after Screening visit. Neutropenia recorded as an Adverse Event of Special Interest (AESI)

- **Efficacy assessment**
  - **Efficacy measurements**

- Investigator's Global Assessment (IGA) score:

  IGA assessed at Screening, Baseline, Week 4, Week 8, and Week 12/Early Termination (ET) visits

- Inflammatory lesion count:

  Inflammatory lesion counts at Screening, Baseline, Week 4, Week 8, and Week 12/ET visits.

- Efficacy criteria

Efficacy measured as Success (i.e. at least 2-grade improvement in IGA) plus statistically significant change in inflammatory lesion counts from Baseline

- **Pharmacokinetics assessment**
  - Plasma levels assessments:

    Plasma levels (C_t) of CD5024 and its 2 main metabolites, M1 and M2, determined under fasting conditions between 8:00 AM and 11:00 AM following 2, 4, 6, 8, 10, and 12 weeks of treatment and 4 weeks after treatment discontinuation.

- **Principal statistical methods**
  - Safety assessments
    - Frequency of neutropenia (defined as NCC ≤ 1.5 GigaCells/L)
    - NCC
    - Other laboratory data
    - Incidence of adverse events, vital signs, physical examination

  - Other endpoints
    - CD5024 PK parameters : C_t at each visit from Week 2,
    - M1 and M2 PK parameter: C_t at each visit from Week 2 if appropriate.

  - Co-primary efficacy endpoints:
    - Success Rate based on IGA
    - Inflammatory Lesion Count

  - Secondary efficacy endpoints:
    - Percent change from Baseline in lesion counts
- **Results**
  - Demographics and baseline disease characteristics

Table 1 Demographic Data

		CD5024 1%	Vehicle	Total
Subjects Screened	N	-	-	304
Intent-to-Treat Population	N	104	106	210
Per-Protocol Population	N	95	91	186
Safety Population	N	104	106	210
Gender	N	104	106	210
	Male	34 (32.7%)	32 (30.2%)	66 (31.4%)
	Female	70 (67.3%)	74 (69.8%)	144 (68.6%)
Age (years)	N	104	106	210
	Mean±SD	55.4 ± 12.9	55.4 ± 12.3	55.4 ± 12.6
	Median	57.5	56.5	57.0
	(Min,Max)	(23,80)	(25,81)	(23,81)
Race	N	104	106	210
	Caucasian	104 (100.0%)	105 (99.1%)	209 (99.5%)
	Asian	0 (0.0%)	1 (0.9%)	1 (0.5%)

Data Source: Section 14.1, Table 14.1.4.

Treatment groups were comparable with respect to demographic characteristics. Overall, 68.6% of subjects were females, mean age was 55.4 years (in both treatment groups), and 99.5% were Caucasians (Table 1).

Table 2 Baseline Disease Characteristics

		CD5024 1%	Vehicle
IGA at Baseline	N	104	106
	3 - Moderate	84 (80.8%)	85 (80.2%)
	4 - Severe	20 (19.2%)	21 (19.8%)
Papules	N	104	106
	Mean±SD	26.4 ± 14.0	30.0 ± 24.9
	Median	24.0	22.0
	(Min,Max)	(7,96)	(7,199)
Pustules	N	104	106
	Mean±SD	8.9 ± 9.5	10.0 ± 9.9
	Median	6.0	6.5
	(Min,Max)	(0,62)	(0,59)
Inflammatory lesion counts	N	104	106
	Mean±SD	35.2 ± 17.0	40.0 ± 28.1
	Median	31.0	30.0
	(Min,Max)	(15,102)	(15,211)

Data Source: Section 14.2, Table 14.2.1.1.

In accordance with protocol requirements, all participants had an IGA at Baseline of 3 (moderate) or 4 (severe) and had a Baseline inflammatory lesion count of at least 15 lesions. Approximately 80% of subjects in both treatment groups had an IGA score of 3 at Baseline. The median inflammatory lesion count was 31.0 in the CD5024 treatment group and 30.0 in the vehicle group (Table 2).

- Efficacy
  - The observed Success Rates based on IGA score (defined as the percentage of subjects who achieved at least a 2-grade improvement from Baseline) were 55.8% for CD5024 1% and 34.0% for the CD5024 Vehicle at Week 12-LOCF and the p-value was equal to 0.002, indicating that there was a statistically significant difference between the groups. The difference occurred as soon as Week 4-LOCF and was sustained through Week 12-LOCF. The PP analysis of the success rate based on a minimum 2-grade improvement from Baseline confirmed the superiority of CD5024 1% cream over its vehicle at all measurement time points ($p \leq 0.009$).

Table 3 Success rate at Week 12 Defined as Subjects Who Achieved 2-Grade Improvement from Baseline Based on IGA Score (ITT-LOCF)

		CD5024 1%	Vehicle	p-value [a]
Baseline	**N**	104	106	
	3 - Moderate	84 (80.8%)	85 (80.2%)	
	4 - Severe	20 (19.2%)	21 (19.8%)	
Week 4-LOCF	**N**	104	106	<0.001
	Success	18 (17.3%)	3 (2.8%)	
	Failure	86 (82.7%)	103 (97.2%)	
Week 8-LOCF	**N**	104	106	0.001
	Success	35 (33.7%)	15 (14.2%)	
	Failure	69 (66.3%)	91 (85.8%)	
Week 12-LOCF	**N**	104	106	0.002
	Success	58 (55.8%)	36 (34.0%)	
	Failure	46 (44.2%)	70 (66.0%)	

[a] p-values based on CMH test stratified by analysis-centre, using general association.
Data Source: Section 14.2, Table 14.2.2.5.

When defining the success in terms of subjects who achieved Clear or Almost clear status, the success rates were 48.1% for CD5024 1% and 32.1% for vehicle at Week 12-LOCF ($p = 0.018$) (Table 4). The difference occurred as early as Week 4-LOCF ($p < 0.001$) and was sustained till Week 12-LOCF. The PP analysis of the success rate based on achievement of Clear or Almost clear status confirmed the statistically significant superiority of CD5024 1% cream over its vehicle at Week 4 ($p = 0.001$), but not at Week 8 ($p = 0.060$) or Week 12 ($p = 0.059$).

Table 4 Success rate at Week 12 Defined as Subjects who Achieved Clear or Almost Clear Status Based on IGA Score (ITT-LOCF)

		CD5024 1%	Vehicle	p-value [a]
Baseline	**N**	104	106	
	3 - Moderate	84 (80.8%)	85 (80.2%)	
	4 - Severe	20 (19.2%)	21 (19.8%)	
Week 4-LOCF	**N**	104	106	<0.001
	Success	14 (13.5%)	1 (0.9%)	
	Failure	90 (86.5%)	105 (99.1%)	
Week 8-LOCF	**N**	104	106	0.023
	Success	27 (26.0%)	14 (13.2%)	
	Failure	77 (74.0%)	92 (86.8%)	
Week 12-LOCF	**N**	104	106	0.018
	Success	50 (48.1%)	34 (32.1%)	
	Failure	54 (51.9%)	67.9%)	

[a] p-values based on CMH test stratified by analysis-centre, using general association.
Data Source: Section 14.2, Table 14.2.2.7.

Both treatment groups had reduced inflammatory lesion counts compared to Baseline at each post-Baseline visit. At Endpoint (Week 12-LOCF), the median percent reduction from Baseline was 82% with CD5024 1% and 64% with the vehicle based on the ITT population. The difference between the two treatments was statistically significant at Week 12-LOCF for both absolute change and percent change from Baseline ($p = 0.001$ and $p < 0.001$, respectively); it occurred as early as Week 4-LOCF ($p = 0.031$and $p = 0.023$ for absolute and percent change from Baseline, respectively) and was sustained to the end of the treatment period (Table 5).

Table 5 Summary of the Inflammatory Lesion Counts at Week 12 (ITT-LOCF)

		CD5024 1%			Vehicle			p-value	
		Raw Data	Change from Baseline	Percent Change from Baseline	Raw Data	Change from Baseline	Percent Change from Baseline	Change from Baseline [a]	Percent Change from Baseline[b]
Baseline	**N**	104	0	0	106	0	0		
	Mean±SD	35.2 ± 17.0			40.0 ± 28.1				
	Median	31			30				
	(Min,Max)	(15,102)			(15,211)				
	(Q1,Q3)	(23,43)			(23,48)				
Week 4 - LOCF	**N**	104	104	104	106	106	106	0.031	0.023
	Mean±SD	20.1 ± 16.1	-15.1 ± 14.7	-42.3 ± 30.2	27.3 ± 25.1	-12.7 ± 12.4	-32.4 ± 28.5		
	Ls (mean)±SE		-16.1 ± 1.2			-12.6 ± 1.2			
	Median	16	-14	-46	20	-11	-33		
	(Min,Max)	(1,102)	(-95,16)	(-99,42)	(0,200)	(-51,16)	(-100,50)		
	(Q1,Q3)	(10,24)	(-22,-7)	(-67,-22)	(13,36)	(-19,-5)	(-53,-12)		
Week 8 - LOCF	**N**	104	104	104	106	106	106	<0.001	<0.001
	Mean±SD	12.1 ± 13.2	-23.2 ± 15.0	-65.2 ± 25.9	21.5 ± 23.4	-18.5 ± 16.4	-46.2 ± 32.8		
	Ls(mean)±SE		-25.0 ± 1.2			-18.9 ± 1.2			
	Median	9	-22	-74	16	-16	-50		
	(Min,Max)	(0,102)	(-86,16)	(-100,19)	(0,200)	(-76,11)	(-100,73)		
	(Q1,Q3)	(5,15)	(-31,-15)	(-83,-52)	(9,28)	(-25,-7)	(-72,-25)		
Week 12 - LOCF	**N**	104	104	104	106	106	106	0.001	<0.001
	Mean±SD	8.6 ± 11.7	-26.6 ± 15.9	-74.5 ± 25.4	17.2 ± 23.5	-22.8 ± 18.4	-59.3 ± 31.1		
	Ls(mean)±SE		-29.0 ± 1.3			-23.4 ± 1.3			
	Median	5	-25	-82	11	-20	-64		
	(Min,Max)	(0,102)	(-84,16)	(-100,19)	(0,200)	(-96,8)	(-100,25)		
	(Q1,Q3)	(2,12)	(-37,-16)	(-93,-64)	(5,21)	(-29,-12)	(-84,-44)		

(a) p-values based on ANCOVA including treatments and analysis-centre as factors and baseline as covariate

(b) p-values based on CMH test stratified by analysis-centre with ridit transformation and row mean score difference statistic.

Data Source: Section 14.2, Table 14.2.2.9.

Concerning the PP population, the difference between the CD5024 and vehicle treatment groups was statistically significantly in favour of CD5024 1% for both absolute change from Baseline in inflammatory lesion counts and percent change from Baseline at all assessment visits.

- Safety
  - Adverse Events

Table 6 Overview of Treatment-Emergent Adverse Events

	CD5024 1% QD (N=104)		CD5024 Vehicle (N=106)	
	nb events	nb(%) subject	nb events	nb(%) subject
All AEs	110	57 (54.8%)	107	63 (59.4%)
Related AEs	6	5 (4.8%)	5	5 (4.7%)
Neutropenia	3	3 (2.9%)	1	1 (0.9%)
Related Neutropenia	0	0 (0.0%)	0	0 (0.0%)
All dermatologic AEs	22	13 (12.5%)	12	10 (9.4%)
Related dermatologic AEs	6	5 (4.8%)	5	5 (4.7%)
All serious AEs	6	4 (3.8%)	3	2 (1.9%)
Related serious AEs	0	0 (0.0%)	0	0 (0.0%)
All severe AEs	3	2 (1.9%)	0	0 (0.0%)
Related severe AEs	0	0 (0.0%)	0	0 (0.0%)
All AEs of Special Interest	4	4 (3.8%)	3	3 (2.8%)
Related AEs of Special Interest	1	1 (1.0%)	2	2 (1.9%)
All AEs leading to discontinuation	2	2 (1.9%)	1	1 (0.9%)
Related AEs leading to discontinuation	0	0 (0.0%)	1	1 (0.9%)
Deaths	0	0 (0.0%)	0	0 (0.0%)

Adverse events are defined as events occurring the day of the first use of medication or after, with exception of those reported from lab data because the blood sample was to be drawn before the time of first application.

Numbers in columns cannot be added because a given subject may have reported more than one AE.

Data source: Section 14.3, Table 14.3.2.1

Overall, the percentages of subjects with at least one treatment-emergent AE (TEAE) were 54.8% and 59.4% for CD5024 1% cream and vehicle, respectively (Table 6). As for the related TEAEs, the corresponding percentages were 4.8% (CD5024 1% cream) and 4.7% (vehicle). Six (6) subjects had treatment-emergent SAEs (4 subjects in the CD5024 1% group and 2 subjects in the vehicle group). No treatment-emergent SAEs were considered to be related to study drug.

As can be seen in Table 7, all TEAEs deemed related to study treatment by the Investigator were mild in intensity and dermatological in nature. Erythema was the most frequently reported related TEAE (3.8% of subjects for CD5024 1% and 2.8% of subjects for vehicle).

Table 7 Summary of Related Treatment-Emergent Adverse Events by Preferred Term (Safety population)

	CD5024 1% QD (N= 104)				CD5024 Vehicle (N= 106)			
	Missing	Mild	Moderate	Severe	Missing	Mild	Moderate	Severe
TOTAL NUMBER OF AEs	0	6	0	0	0	5	0	0
TOTAL NUMBER (%) OF SUBJECTS WITH AEs	-	5(4.8%)	-	-	-	5(4.7%)	-	-
Skin and subcutaneous tissue disorders	-	5(4.8%)	-	-	-	5(4.7%)	-	-
- Dry skin	-	-	-	-	-	1(0.9%)	-	-
- Erythema	-	4(3.8%)	-	-	-	3(2.8%)	-	-
- Skin irritation	-	1(1.0%)	-	-	-	1(0.9%)	-	-
- Skin tightness	-	1(1.0%)	-	-	-	-	-	-

Adverse events are defined as events occurred after the first injection

A subject was counted once per preferred term (highest intensity) even if more than one occurrence of the event was experienced

A subject was counted once per system organ class (highest intensity whatever the AE within a system organ class) even if more than one event was experienced within the system organ class

Data Source: Section 14.3, Table 14.3.2.7.

Two (2) subjects (1.9%) in the CD5024 1% group discontinued the study due to TEAEs versus 1 subject (0.9%) in the vehicle group (Table 8). The 2 subjects in the active treatment group discontinued due to "deterioration of rosacea symptoms" and "worsening of lymphocytic vasculitis", respectively. Neither adverse event was related to the study drug. One subject in the vehicle group discontinued the study due to "arteriovenous malformation", the onset of which occurred 7 days before the first application (thus, this discontinuation does not appear in Table 6). One (1) subject (0.9%) in the vehicle group discontinued permanently due to mild "irritative dermatitis" considered related to treatment.

Table 8 Summary of Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term (Safety Population)

			System Organ				Date of	
Treatment	**Subject Number**	**TEAE**	**Class/ Preferred Term/ Verbatim Term**	**Severity**	**Serious**	**Causality**	**Start**	**Stop**
CD5024 1%	5567-011	Yes	Skin and subcutaneous tissue disorders/ Rosacea/ DETEROIATION OF THE ROSACEA SYMPTOMS	Moderate	No	Not Related	2011-01-19	
	5668-003	Yes	Vascular disorders/ Vasculitis/ WORSENING OF LYMPHOCYTIC VASCULITIS	Severe	Yes	Not Related	2011-01-24	2011-03-21
Vehicle	5557-011	No	Congenital, familial and genetic disorders/ Arteriovenous malformation/ ARTERIOVENOUS MALFORMATION AT THE SITE OF LEFT CAROTID ARTERY BIFURCATION	Severe	Yes	Not Related	2010-12-20	2011-02-07
	5563-002	Yes	Skin and subcutaneous tissue disorders/ Skin irritation/ IRRITATIVE DERMATITIS	Mild	No	Related	2010-12-09	2010-12-21

Data Source: Section 14.3, Table 14.3.2.8.

There were 7 AESIs involving 7 subjects that were reported in the treatment period: 4 AESIs in the CD5024 group and 3 AESIs in the vehicle group. One (1) AESI in the CD5024 group (skin irritation) and 2 AESIs in the vehicle group (skin irritation and facial redness) were considered to be related to study treatment.

The 4 remaining subjects who were reported with treatment-emergent AESIs had occurrences of NCCs below 1.5 G/L; 3 subjects were in the CD5024 treatment group and 1 subject was in the vehicle group. These TEAEs were one-time, single observations for each of the four subjects.

- Neutrophil Cell Counts

The number of subjects with NCCs above, below, or within the normal range was computed for each study visit and also in terms of the lowest observed post-Baseline value (Table 9).

Table 9 Neutrophil Counts Distribution According to Laboratory Normal Ranges and to Threshold of 1.5 G/L

Time point	Neutrophils (10^9/L)	CD5024 1% N (%)	Vehicle N (%)
Week -4	[2.1-6.9]	104 (100.0)	104 (99.05)
	>6.9	0(0.0%)	1 (0.95)
Week -2	<= 1.5	0(0.0%)	1 (0.97)
	[2.1-6.9]	98 (100.0)	102 (99.03)
Baseline	<= 1.5	2 (1.92)	0(0.0%)
	]1.5-2.1[	5 (4.81)	2 (1.89)
	[2.1-6.9]	93 (89.42)	104 (98.11)
	>6.9	4 (3.85)	0(0.0%)
Week 2	]1.5-2.1[	8 (8.16)	3 (3.03)
	[2.1-6.9]	88 (89.80)	95 (95.96)
	>6.9	2 (2.04)	1 (1.01)
Week 4	]1.5-2.1[	5 (5.15)	5 (5.21)
	[2.1-6.9]	89 (91.75)	88 (91.67)
	>6.9	3 (3.09)	3 (3.13)
Week 6	<= 1.5	2 (2.04)	1 (1.03)
	]1.5-2.1[	9 (9.18)	9 (9.28)
	[2.1-6.9]	84 (85.71)	86 (88.66)
	>6.9	3 (3.06)	1 (1.03)
Week 8	]1.5-2.1[	5 (5.15)	1 (1.03)
	[2.1-6.9]	88 (90.72)	94 (96.91)
	>6.9	4 (4.12)	2 (2.06)
Week 10	<= 1.5	1 (1.02)	0(0.0%)
	]1.5-2.1[	5 (5.10)	0(0.0%)
	[2.1-6.9]	89 (90.82)	93 (95.88)
	>6.9	3 (3.06)	4 (4.12)
Week 12/Final	]1.5-2.1[	6 (5.88)	5 (4.72)
	[2.1-6.9]	94 (92.16)	100 (94.34)
	>6.9	2 (1.96)	1 (0.94)

Table 9 Neutrophil Counts Distribution According to Laboratory Normal Ranges and to Threshold of 1.5 G/L

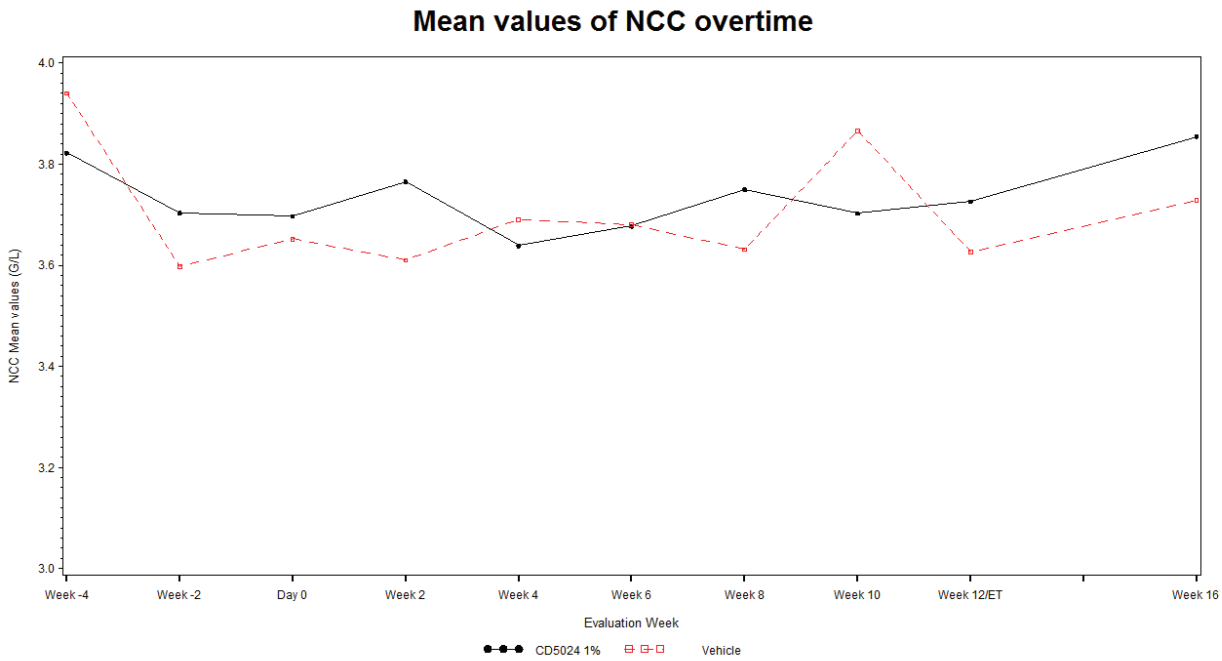
Time point	Neutrophils (10^9/L)	CD5024 1% N (%)	Vehicle N (%)
Week 16	]1.5-2.1[	5 (5.05)	1 (1.04)
	[2.1-6.9]	91 (91.92)	94 (97.92)
	>6.9	3 (3.03)	1 (1.04)
Lowest post-Baseline value	<= 1.5	4 (3.88)	1 (0.94)
	]1.5-2.1[	22 (21.36)	17 (16.04)
	[2.1-6.9]	77 (74.76)	88 (83.02)

Baseline is the last observed pre-treatment value
Data Source: Section 14.3, Table 14.3.3.2.1.

Overall, there were 5 subjects reported with NCCs below 1.5 G/L, 4 (3.9%) in the CD5024 1% group and 1 (0.9%) in the vehicle group (Table 9, Lowest post-Baseline value). One of these subjects in the active treatment group also had an NCC below 1.5 G/L at Baseline prior to treatment; a retest performed two days later (after one application of study drug) also produced a low NCC and this subject discontinued study participation. Subsequent NCCs obtained at two re-tests were all within the normal range. Therefore, four subjects had single treatment-emergent NCCs below 1.5 G/L.

Mean NCCs for all subjects were similar at Baseline for both treatment groups, i.e. around 3.7 G/L (Table 10). Over time, the means remained stable and similar between treatments (Figure 1).

Figure 1 Mean Values of NCC Over Time



Data Source : Section 14.3, Figure 14.3.3.2.18.

Percent changes from Baseline in NCCs were compared at each post-Baseline visit between CD5024 1% and its vehicle, and also for the lowest value observed after Baseline (retests and unscheduled visits included). As seen in Table 10, at each time point, no between-group differences were observed (all p-values ≥0.21).

Table 10 Descriptive Statistics of the Change and Percent Change from Baseline in Neutrophil Counts

		CD5024 1% QD			CD5024 Vehicle			p-value
		Raw Data	Change from Baseline	Percent Change from Baseline	Raw Data	Change from Baseline	Percent Change from Baseline	Percent Change from Baseline
Week -4	N	104			105			
	Mean±SD	3.82 ± 1.05			3.94 ± 1.16			
	Median	3.65			3.75			
	(Min,Max)	(2.11,6.84)			(2.13,7.76)			
	(Q1,Q3)	(3.07,4.50)			(3.05,4.70)			
Week -2	N	98			103			
	Mean±SD	3.70 ± 1.06			3.60 ± 1.04			
	Median	3.58			3.39			
	(Min,Max)	(2.11,6.78)			(1.30,6.10)			
	(Q1,Q3)	(2.85,4.50)			(2.83,4.30)			
Day 0	N	91			95			
	Mean±SD	3.70 ± 1.49			3.65 ± 1.14			
	Median	3.38			3.48			
	(Min,Max)	(1.35,9.06)			(2.05,6.52)			
	(Q1,Q3)	(2.60,4.24)			(2.76,4.18)			
Baseline*	N	104			106			
	Mean±SD	3.70 ± 1.03			3.70 ± 0.90			
	Median	3.52			3.60			
	(Min,Max)	(1.89,7.08)			(2.09,5.89)			
	(Q1,Q3)	(2.94,4.15)			(2.97,4.34)			
Week 2	N	98	98	98	99	99	99	0.542
	Mean±SD	3.77 ± 1.30	0.04 ± 0.99	2.13 ± 26.95	3.61 ± 1.04	-0.09 ± 0.83	-1.11 ± 22.57	
	Median	3.72	-0.02	-0.45	3.50	-0.14	-3.27	
	(Min,Max)	(1.67,9.27)	(-2.12,4.30)	(-48.85,86.67)	(1.95,7.13)	(-2.52,2.02)	(-43.19,64.13)	
	(Q1,Q3)	(2.76,4.44)	(-0.59,0.60)	(-17.61,17.37)	(2.71,4.23)	(-0.59,0.36)	(-15.92,10.91)	
Week 4	N	97	97	97	96	96	96	0.612
	Mean±SD	3.64 ± 1.20	-0.12 ± 0.82	-2.39 ± 21.31	3.69 ± 1.21	-0.01 ± 0.92	0.47 ± 24.68	
	Median	3.59	-0.05	-1.65	3.60	-0.14	-3.97	
	(Min,Max)	(1.57,8.07)	(-2.03,2.88)	(-41.64,80.53)	(1.71,7.19)	(-2.23,2.88)	(-53.51,68.29)	
	(Q1,Q3)	(2.84,4.19)	(-0.61,0.24)	(-16.06,7.98)	(2.87,4.30)	(-0.66,0.47)	(-15.98,14.77)	
Week 6	N	98	98	98	97	97	97	0.745
	Mean±SD	3.68 ± 1.41	-0.06 ± 1.14	-0.35 ± 31.22	3.68 ± 1.30	-0.04 ± 1.03	-1.04 ± 26.55	
	Median	3.51	-0.15	-4.88	3.64	-0.06	-1.79	
	(Min,Max)	(0.96,9.06)	(-2.71,4.86)	(-62.47,126.27)	(1.46,10.30)	(-1.77,6.07)	(-42.45,143.57)	
	(Q1,Q3)	(2.73,4.44)	(-0.69,0.41)	(-20.04,10.71)	(2.79,4.24)	(-0.54,0.34)	(-15.15,12.36)	
Week 8	N	97	97	97	97	97	97	0.678
	Mean±SD	3.75 ± 1.26	0.02 ± 0.94	1.87 ± 25.82	3.63 ± 1.10	-0.05 ± 0.95	0.22 ± 26.68	
	Median	3.61	-0.07	-1.66	3.44	-0.08	-2.04	
	(Min,Max)	(2.00,7.87)	(-2.05,3.09)	(-43.89,111.79)	(2.09,7.98)	(-3.38,5.01)	(-57.39,168.71)	
	(Q1,Q3)	(2.84,4.49)	(-0.49,0.44)	(-15.60,13.15)	(2.73,4.26)	(-0.60,0.39)	(-14.74,11.16)	

Table 10 Descriptive Statistics of the Change and Percent Change from Baseline in Neutrophil Counts

		CD5024 1% QD			CD5024 Vehicle			p-value
		Raw Data	Change from Baseline	Percent Change from Baseline	Raw Data	Change from Baseline	Percent Change from Baseline	Percent Change from Baseline
Week 10	N	98	98	98	97	97	97	0.210
	Mean±SD	3.70 ± 1.28	-0.02 ± 1.00	0.50 ± 25.90	3.87 ± 1.20	0.18 ± 0.99	6.45 ± 27.64	
	Median	3.60	-0.06	-1.87	3.58	0.01	0.25	
	(Min,Max)	(0.97,8.95)	(-3.39,4.23)	(-64.14,120.83)	(2.15,7.34)	(-1.99,3.86)	(-36.56,112.36)	
	(Q1,Q3)	(2.91,4.25)	(-0.63,0.41)	(-15.71,12.16)	(3.03,4.44)	(-0.43,0.62)	(-12.18,19.36)	
Week 12/Final	N	102	102	102	106	106	106	0.892
	Mean±SD	3.70 ± 1.17	-0.03 ± 0.92	0.86 ± 24.49	3.68 ± 1.14	-0.02 ± 0.98	1.26 ± 27.13	
	Median	3.61	-0.15	-4.02	3.58	-0.17	-4.53	
	(Min,Max)	(1.71,9.11)	(-2.00,4.68)	(-52.73,105.48)	(1.81,10.30)	(-1.88,6.07)	(-43.35,143.57)	
	(Q1,Q3)	(2.90,4.37)	(-0.60,0.52)	(-15.20,14.80)	(2.96,4.18)	(-0.60,0.42)	(-15.98,12.85)	
Week 16	N	99	99	99	96	96	96	0.722
	Mean±SD	3.85 ± 1.36	0.13 ± 1.22	5.87 ± 35.78	3.73 ± 1.02	0.04 ± 0.70	2.28 ± 20.75	
	Median	3.66	-0.07	-2.02	3.60	0.02	0.58	
	(Min,Max)	(1.58,10.31)	(-2.15,7.13)	(-38.73,224.61)	(1.78,6.97)	(-1.29,2.07)	(-36.16,98.76)	
	(Q1,Q3)	(2.95,4.47)	(-0.57,0.54)	(-14.08,20.02)	(2.96,4.37)	(-0.44,0.48)	(-10.39,14.41)	
Lowest post baseline value	N	103	103	103	106	106	106	0.293
	Mean±SD	2.80 ± 0.88	-0.91 ± 0.70	-23.86 ± 16.18	2.90 ± 0.84	-0.81 ± 0.69	-20.97 ± 16.33	
	Median	2.73	-0.87	-24.36	2.75	-0.82	-22.28	
	(Min,Max)	(0.96,5.46)	(-3.39,0.73)	(-64.14,18.62)	(1.46,5.77)	(-3.38,1.03)	(-57.39,24.38)	
	(Q1,Q3)	(2.08,3.51)	(-1.28,-0.48)	(-34.20,-15.26)	(2.29,3.35)	(-1.21,-0.40)	(-32.93,-12.14)	

*Baseline is based on the by subject, geometric mean of the observed pre-treatment values
p-value for percent change from Baseline: Cochran-Mantel-Haenszel test using row mean score difference and ridit transformation.
Data Source: Section 14.3, Table 14.3.3.2.2.

Under treatment, the maximum decrease in the median percent change from Baseline in NCCs occurred at Week 6 in CD5024 1% group and at Week 12/Final in the vehicle group, with median percent changes from Baseline of 4.88% and 4.53% respectively in these groups at these time points. In CD5024 1% group, the maximum decrease at Week 12/Final was 4.02% (Table 10).

Neutrophil count variations observed during treatment were categorized in terms of decrease or increase from Baseline, by categories (i.e. less than 30% variation, 30% to 50% variation, and more than 50% variation) (Table 11).

At Week 12/Final value under treatment:

- Fifty-eight (58) subjects (56.9%) had a decrease of NCC in the CD5024 1% group. Among these, a decrease of more than 30% was observed in 4 subjects (3.9%);
- Sixty (60) subjects (56.6%) had a decrease of NCC in the vehicle group. Among these, a decrease of more than 30% was observed in 6 subjects (5.7%).

Given the close similarity between the active drug and the vehicle groups with respect to frequencies of decrease in NCC, the results suggest that the decreases in NCC were not due to the presence of CD5024.

Table 11 Distribution of Percent Change from Baseline Over Time

			CD5024 1% QD		CD5024 Vehicle	
			N	%	N	%
Week 2	Decrease	]-50%;-30%]	7	7.1	7	7.1
		]-30%; 0%[	43	43.9	52	52.5
		N	50	51.0	59	59.6
	Increase	0%;42.9%[	41	41.8	34	34.3
		[42.9%;100%[	7	7.1	6	6.1
		N	48	49.0	40	40.4
	N		98	100.0	99	100.0
Week 4	Decrease	<=-50%			1	1.0
		]-50%;-30%]	9	9.3	5	5.2
		]-30%; 0%[	46	47.4	49	51.0
		N	55	56.7	55	57.3
	Increase	0%;42.9%[	39	40.2	35	36.5
		[42.9%;100%[	3	3.1	6	6.3
		N	42	43.3	41	42.7
	N		97	100.0	96	100.0
Week 6	Decrease	<=-50%	3	3.1	0	
		]-50%;-30%]	9	9.2	13	13.4
		]-30%; 0%[	44	44.9	41	42.3
		N	56	57.1	54	55.7
	Increase	0%;42.9%[	34	34.7	40	41.2
		[42.9%;100%[	6	6.1	2	2.1
		>=100%	2	2.0	1	1.0
		N	42	42.9	43	44.3
	N		98	100.0	97	100.0
Week 8	Decrease	<=-50%			1	1.0
		]-50%;-30%]	6	6.2	3	3.1
		]-30%; 0%[	47	48.5	50	51.5
		N	53	54.6	54	55.7
	Increase	0%;42.9%[	40	41.2	39	40.2
		[42.9%;100%[	3	3.1	3	3.1
		>=100%	1	1.0	1	1.0
		N	44	45.4	43	44.3
	N		97	100.0	97	100.0

Table 11 Distribution of Percent Change from Baseline Over Time

			CD5024 1% QD		CD5024 Vehicle	
			N	%	N	%
Week 10	Decrease	<=-50%	1	1.0	0	
		]-50%;-30%]	7	7.1	4	4.1
		]-30%; 0%[	44	44.9	43	44.3
		N	52	53.1	47	48.5
	Increase	0%;42.9%[	41	41.8	42	43.3
		[42.9%;100%[	4	4.1	6	6.2
		>=100%	1	1.0	2	2.1
		N	46	46.9	50	51.5
	N		98	100.0	97	100.0
Week 12/Final	Decrease	<=-50%	1	1.0	0	
		]-50%;-30%]	3	2.9	6	5.7
		]-30%; 0%[	54	52.9	54	50.9
		N	58	56.9	60	56.6
	Increase	0%;42.9%[	39	38.2	38	35.8
		[42.9%;100%[	4	3.9	7	6.6
		>=100%	1	1.0	1	0.9
		N	44	43.1	46	43.4
	N		102	100.0	106	100.0
Week 16	Decrease	]-50%;-30%]	6	6.1	3	3.1
		]-30%; 0%[	51	51.5	44	45.8
		N	57	57.6	47	49.0
	Increase	0%;42.9%[	33	33.3	47	49.0
		[42.9%;100%[	7	7.1	2	2.1
		>=100%	2	2.0	0	
		N	42	42.4	49	51.0
	N		99	100.0	96	100.0
Lowest post-Baseline value	Decrease	<=-50%	6	5.8	2	1.9
		]-50%;-30%]	28	27.2	28	26.4
		]-30%; 0%[	61	59.2	63	59.4
		N	95	92.2	93	87.7
	Increase	0%;42.9%[	8	7.8	13	12.3
		N	8	7.8	13	12.3
	N		103	100.0	106	100.0

Baseline is based on the by subject, geometric mean of the observed pre-treatment values
Data Source: Section 14.3, Table 14.3.3.2.3.

Among the subjects who had normal neutrophil counts before the first application of investigational product, 87 subjects (94.6%) in CD5024 1% group and 98 subjects (94.2%) in the vehicle group were still within normal range at Week 12/Final visit under treatment, while 4 subjects (4.3%) in CD5024 1% group and 5 subjects (4.8%) in the vehicle group shifted from normal values at Baseline to values below 2.1 G/L, the lower limit of the normal range (see upper part of Table 12).

Forty (40) subjects with neutrophil cell counts within the normal range before first application experienced a decrease in counts below the lower limit of the normal range at some time during treatment (22 subjects in the CD5024 1% group and 18 subjects in the vehicle group) (see lower part of Table 12).

When looking at lowest observed value while on treatment (see lower part of Table 12), 3 subjects out of 92 (3.3%) had a value below 1.5 G/L in the CD5024 1% group, whereas they were within normal range before treatment (Subject 5140-009, 0.96 G/L at Week 6; subject 5668-004, 1.42 G/L at Week 6; and subject 5532-003, 0.97 G/L at Week 10), against one subject out of 104 (1.0%) in the vehicle group (Subject 5563-003, 1.46 G/L at Week 6). Notably, the treatment-emergent cases of NCC below 1.5 G/L occurred at only a single time point in the study.

Table 12 NCC shift tables between pre-treatment and values under treatment

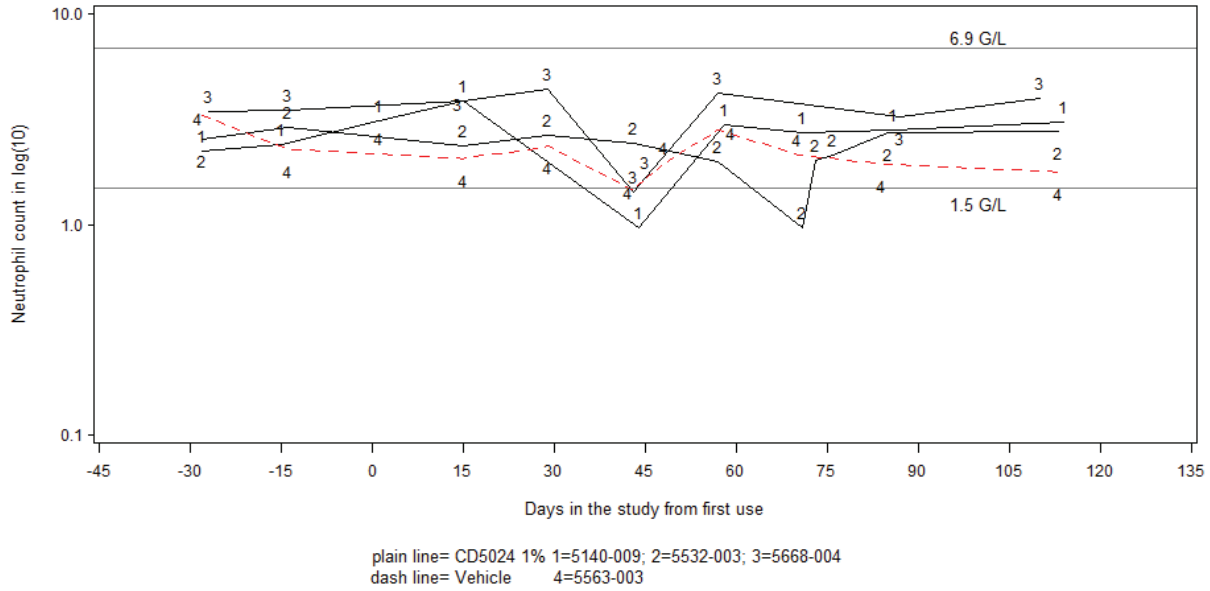
in G/L		Baseline									
		CD5024 1% QD					CD5024 Vehicle				
		<=1.5	]1.5-2.1[	[2.1-6.9]	>6.9	Missing	<=1.5	]1.5-2.1[	[2.1-6.9]	>6.9	Missing
Week 12/Final	]1.5-2.1[	1(100.0%)	1(20.0%)	4(4.3%)	0	0	0	0	5(4.8%)	0	0
	[2.1-6.9]	0	4(80.0%)	87(94.6%)	3(75.0%)	0	0	2(100.0%)	98(94.2%)	0	0
	>6.9	0	0	1(1.1%)	1(25.0%)	0	0	0	1(1.0%)	0	0
	Missing	1	0	1	0	0	0	0	0	0	0
Lowest post-Baseline value	<= 1.5	1(50.0%)	0	3(3.3%)	0	0	0	0	1(1.0%)	0	0
	]1.5-2.1[	1(50.0%)	2(40.0%)	19(20.7%)	0	0	0	0	17(16.3%)	0	0
	[2.1-6.9]	0	3(60.0%)	70(76.1%)	4(100.0%)	0	0	2(100.0%)	86(82.7%)	0	0
	Missing	0	0	1	0	0	0	0	0	0	0

Baseline is the last observed pre-treatment value
Data Source: Section 14.3, Table 14.3.3.2.4.

Among these 4 “treatment emergent” cases of NCCs <1.5 G/L, the NCC count had normalized under treatment for 3 cases and after a temporary discontinuation of the treatment in the other case (Subject 5140-009). In this subject from the CD5024 1% group, study drug was temporarily stopped (as specified in the protocol) due to the presence of infectious signs and re-administered after normalization of the NCC at retest, without any recurrence of the neutropenia.

The individual NCC results over time in the subjects reported with treatment-emergent values below 1.5 G/L are shown in Figure 2. No relationship was observed between occurrence of NCCs below 1.5 G/L and time of occurrence of this finding.

Figure 2 **Plot of Neutrophil count versus blood sampling day for subjects with NCC <1.5 G/L**



Data Source : Galderma internal communication

No subject reported severe (<0.5 G/L) neutropenia. At no point during the study did the IDMC consider it necessary to unblind the data or to definitely stop the treatment. All cases of NCC ≤1.5 G/L were assessed as 'not related' to the study drug by the IDMC and by the investigators.

Temperature loggers were included in the sample shipment boxes to monitor temperature as routine practice. Conditions of transport established by the central lab were intended to be between 4 and 37°C.

During shipment to the central laboratory, more than 54% (1021 of 1871) of the blood samples experienced a temperature below 4°C, evenly balanced between treatments: 53.7% (CD5024 1%) and 55.4% (Vehicle).

Neutrophil cell counts below 2.1 G/L were reported in 7.8% of samples exposed to a temperature below 4°C, versus only approximately 2% of samples not exposed to this low temperature during shipment. This decrease in NCCs with temperatures below 4°C suggests that shipping conditions produced degradation of some blood samples.

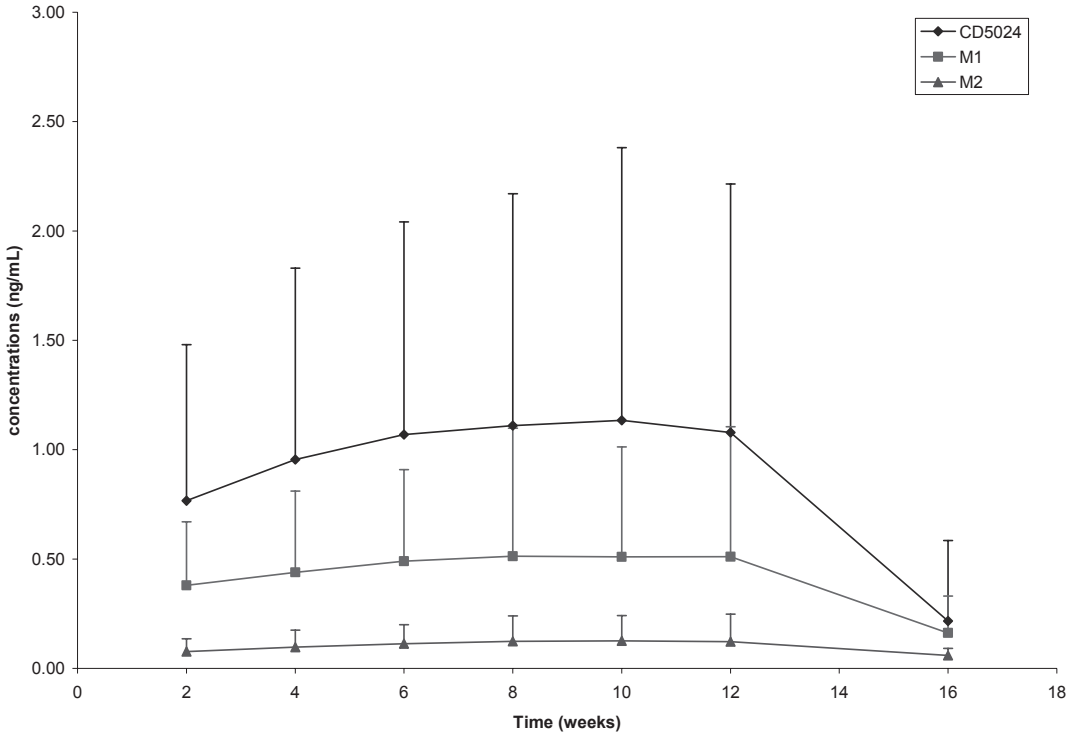
- Pharmacokinetics

Of the 104 subjects randomized to receive CD5024 1% cream, plasma samples from 101 subjects were evaluable for PK analyses. Assessment of CD5024 systemic exposure showed mean plasma concentrations ranging from 0.77 ± 0.71 ng/mL to 1.134 ± 1.247 ng/mL (min: 0.05 ng/mL to max: 6.75 ng/mL) throughout the duration of treatment. In addition, systemic exposure remained stable during the treatment period (up to 12 weeks) confirming that steady state conditions were reached by 4 weeks of treatment. At the end of treatment, CD5024 was cleared slowly from plasma; at Week 16 (4 weeks after the end of treatment) mean plasma concentrations decreased to 0.213 ± 0.364 ng/mL (min: <0.05 ng/mL to max: 1.86 ng/mL).

Mean M1 concentrations ranged from 0.38 ± 0.29 ng/mL to 0.51 ± 0.59 ng/mL from Week 2 to Week 12 of treatment, respectively. Mean M2 concentrations ranged from 0.073 ± 0.06 ng/mL to 0.12 ± 0.13 ng/mL from Week 2 to Week 12 of treatment, respectively. Concentrations of both metabolites remained stable throughout the treatment period and achieved steady state by 4 weeks of treatment. Four weeks after the end of treatment, mean M1 concentrations decreased to 0.16 ± 0.17 ng/mL and mean M2 concentrations to 0.06 ± 0.03 ng/mL.

The mean plasma profile of CD5024 and its two main metabolites is presented in Figure 3.

Figure 3 Mean Plasma Profile of CD5024 and its Main Metabolites M1 and M2



Non-quantifiable data were replaced by the LOQ (i.e. 0.05 ng/mL for CD5024 and M2 and 0.11 ng/mL for M1)
Data Source: Galderma Internal Communication

Individual neutrophil counts were plotted against plasma concentration data at each visit. For each subject, the lowest neutrophil count post-Baseline and its change from Baseline were separately plotted against the geometric mean of the CD5024 plasma concentration. In all cases, no or a poor correlation was observed between individual subject neutrophil counts and CD5024 plasma concentrations (i.e. the Pearson correlation coefficient "r" ranged between -0.2818 and -0.0025).

In general, subjects presenting NCCs below 1.5 G/L had low systemic exposures to CD5024 in comparison to the overall data, supporting the absence of a relationship between neutropenia and CD5024.

- **Conclusion**

In the present study, 210 subjects received at least one dose of CD5024 1% cream (N = 104) or vehicle (N = 106) over 12 weeks of once daily applications. A potential effect of CD5024 1% cream on neutrophil cell count was assessed, as well as overall safety, exposure, and efficacy.

A total of 4 treatment-emergent observations of NCCs <1.5 G/L were reported in the study: 3 (2.9%) in the CD5024 1% group versus 1 (0.9%) in the vehicle group. Three subjects had NCCs that normalized during treatment and applications were temporarily suspended for the one remaining subject due to the presence of signs of infection. Treatment was re-started for this subject after normalization of the NCC at re-test. None of the cases were assessed as related to the study drug by either the Investigator or the IDMC.

A *post-hoc* review of the NCC data for these four subjects was performed by two external haematologists, including the chairman of the IDMC. They concluded that improper storage conditions were likely the cause of reduced NCC in two cases and that viral infection was probably the cause of the third low NCC.

There were 9 SAEs reported in 6 subjects, of whom 4 subjects received active treatment. None were deemed related to the study treatment. Seven (7) AESIs were observed for 7 subjects during the treatment period; 4 of these subjects received active treatment. Four (4) AESIs concerned the single observations of low NCCs; the remaining 3 AESIs occurred in 1 subject in the CD5024 group (mild skin irritation) and in 2 subjects (mild skin irritation and mild facial redness, respectively) in the vehicle group. Finally, there were two TEAEs (rosacea and vasculitis) in 2 subjects in the CD5024 group, one TEAE (skin irritation counted as an AESI) in one vehicle-treated subject, and one AE (arteriovenous malformation reported 7 days before the Baseline visit) in another subject in the vehicle group leading to discontinuation. Of these 4 AEs, only skin irritation (in the vehicle subject) was considered related to study treatment.

Concerning the efficacy analysis, statistically significant and clinically relevant differences in favour of the CD5024 1% cream were observed from Week 4 to Week 12, both in terms of success rate (defined as a 2-grade improvement on the IGA scale or as "clear" or "almost clear") and in terms of reduction in the absolute number of inflammatory lesions from Baseline.

Systemic exposure data obtained in this study were consistent with previous PK results: mean plasma concentrations ranged from 0.77 ± 0.71 ng/mL to 1.134 ± 1.247 ng/mL (min: 0.05 ng/mL to max: 6.75 ng/mL) and remained stable throughout the treatment period. Steady state was achieved by 4 weeks of treatment. At the end of treatment, CD5024 was cleared slowly from plasma; at Week 16 (4 weeks after the end of treatment) mean plasma concentrations decreased to 0.213 ± 0.364 ng/mL (ranged from <0.05 to 1.9 ng/mL). Mean plasma concentrations of major metabolites M1 and M2 paralleled those of the parent compound. Mean M1 concentrations ranged from 0.38 ± 0.29 ng/mL to 0.51 ± 0.59 ng/mL from Week 2 to Week 12 of treatment, respectively. Mean M2 concentrations ranged from 0.073 ± 0.06 ng/mL to 0.12 ± 0.13 ng/mL from Week 2 to Week 12 of treatment, respectively. Like the parent compound, both metabolites' plasma concentrations remained stable throughout the treatment period and steady state was achieved by 4 weeks of treatment.

No or poor correlations were demonstrated between individual subject NCCs and plasma concentrations of CD5024 at each sampling visit during the treatment period. Subjects with NCCs below 1.5 G/L had low systemic exposures to CD5024 in comparison to the overall data, thereby supporting the absence of relationship between low neutrophil cell counts and CD5024.