Clinical Study Synopsis for Public Disclosure

These results are supplied for informational purposes only in the interest of scientific disclosure. The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups. This information is not intended to substitute for informed medical advice. You should not use this information to diagnose or treat a health problem or disease without consulting with a Healthcare Professional. Before prescribing any product mentioned in this Register, Healthcare Professionals should always refer to the specific approved product labeling information in their country. The results from a single trial may not reflect the overall results and need to be considered in the context of the totality of the available clinical research results for a product.

1. TITLE PAGE

<table>
<tr><td colspan="3">Title of Study
ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR ROSACEA OVER 12 WEEKS.</td></tr>
<tr><td>Project Name
CD5024</td><td>Project Number
575</td><td>Clinical Phase
2</td></tr>
<tr><td colspan="2">Investigational Products
CD5024 0.1%, 0.3% and 1% cream</td><td>Comparator Products
CD5024 vehicle cream
metronidazole (Rozex®) 0.75% cream</td></tr>
<tr><td>Subject Population/Indication
Male or female subjects with papulopustular rosacea with at least 15 inflammatory facial lesions, at least 18 years old, meeting specific inclusion and exclusion criteria.</td><td>Treatment/Study Duration
12 weeks</td><td>Dose
Once daily:
CD5024 0.1%, 0.3%, 1% cream
CD5024 vehicle cream

Twice daily:
CD5024 1% cream
metronidazole 0.75% cream</td></tr>
<tr><td colspan="3">Design
Multi-centre, randomized, investigator blind, multiple dose, parallel-group vehicle and active controlled comparison study.</td></tr>
<tr><td colspan="2">Study Initiation Date
(first Subject enrolled)
30 June 2006</td><td>Study Completion/Termination Date
(last Subject completed)
18 June 2007</td></tr>
<tr><td colspan="3">EUDRACT/IND No.: 2006-001999-20</td></tr>
</table>

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This Clinical Study Report (CSR) complies with the International Conference on Harmonization (ICH) guidance on the structure and contents of clinical study reports E3 Current Step 4 version, dated 30 November 1995.

All data provided to the Investigator (and study staff) or collected during the study and/or reported herein will be regarded as confidential and proprietary in nature and will not be disclosed to any third party without Galderma's written consent.

Appropriate Investigator and/or Responsible Medical officer's signature(s) are filed in **Appendix 16.1.5.**

2. SYNOPSIS

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

METHODOLOGY

Study objective(s):
To select the dose and regimen of CD5024 cream according to the dose-response relationship.

Study design and clinical phase:
12-week, multi-centre, randomized, investigator blinded, parallel-group vehicle and active controlled comparison phase II dose ranging study. Study visits were conducted at Screening, Baseline/Week 0, Week 2, Week 4, Week 6, Week 8, and Week 12.

Study centre(s):
A total of 26 centres in Australia, the Czech Republic, Germany, Hungary, and the Russian Federation screened and randomized subjects.

Number of subjects:
Planned: 270 subjects;
Randomized: 296 subjects.

Diagnosis and Inclusion criteria:
Male or female subjects with papulopustular *rosacea* and at least 15 inflammatory facial lesions, with at least mild erythema, at least 18 years of age, and meeting other specific inclusion and exclusion criteria.

Study period:
From 30 June 2006 (first subject enrolled) to 18 June 2007 (last subject completed).

Investigational products:

Test Product	**CD5024**	**CD5024**	**CD5024**	**CD5024**	**metronidazole**	**CD5024 vehicle**
Dose and Formulation	0.1% cream	0.3% cream	1% cream	1% cream	0.75% cream	0% cream
Dosage regimen	Once daily (QD)	Once daily (QD)	Once daily (QD)	Twice daily (BID)	Twice daily (BID)	Once daily (QD)
Route of administration	Topical application to whole face					
Batch number Europe	575.757/ 03786/1002 575.757/ 03786/1003	575.767/ 03814/1002 575.767/ 03814/1003	575.754/ 03750/1004	575.754/ 03750/1004	6075050 6075016 6075044	575.754P/ 03818/1002 575.754P/ 03818/1003
Batch number Australia	575.757/ 03786/1002	575.767/ 03814/1002	575.754/ 03750/1003	575.754/ 03750/1003	6075016	575.754P/ 03818/1002
Treatment duration	12 weeks					

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

METHODOLOGY (Continued)

Criteria for evaluation:

- **Efficacy**
  - Primary Efficacy Endpoint
    - Percent change at Week 12 from Baseline in inflammatory lesion counts (papules, pustules).
  - Secondary Efficacy Endpoints
    - Change at Week 12 from Baseline in Investigator Global Assessment score 1 (IGA1: composite score of erythema and inflammatory lesions) and Investigator Global Assessment score 2 (IGA2, score of inflammatory lesions only);
    - Success rate at Week 12, success was defined for both IGA1 and IGA2 as clear or almost clear on a 5-point-scale;
    - Change at Week 12 from Baseline in erythema and telangiectasia scores.

- **Safety**

Safety measurements including recording of Adverse Events, of cutaneous signs and symptoms (e.g. dryness, desquamation, pruritus, stinging/burning) scored on a 4-point scale (0-3) and vital signs at Screening, Baseline and Week 12. Clinical laboratory (haematology, blood chemistry and urinalysis) and physical examinations were performed at Screening and Week 12.

- **Systemic Exposure**

Systemic exposure to CD5024 was assessed by plasma levels at Week 4 and 12.

- **Other Assessments**

Health related Quality of Life questionnaires (Dermatology Life Quality Index (DLQI) and EuroQol - 5 Dimensional (EQ5D) and Patient's Satisfaction using a specific self-administered questionnaire.

Principal statistical methods:

- **Efficacy**

The intent to treat (ITT) population using LOCF (last observation carried forward) was the primary population and included all subjects randomized. The primary time point was Week 12/LOCF. The per protocol (PP) population, excluding major deviators and using observed cases only, was analyzed to confirm results on the ITT population.

The primary efficacy analysis on Percent Change in inflammatory lesions was the pairwise comparison of each CD5024 dosage group versus vehicle, using the Cochran-Mantel-Haenszel test (CMH), with analysis centre as strata, row mean score difference statistic and ridit transformation. To minimize multiplicity issues, the interpretation of each test was stepwise, i.e. a dose of CD5024 could be declared significantly more effective than the vehicle (p 0.05), only if all higher CD5024 doses were shown more effective than the vehicle (p 0.05).

The secondary analysis on percent change in inflammatory lesions compared each CD5024 dosage versus metronidazole and used the same tests and principles as described above for the comparison versus vehicle.
All tests were two-sided and a 0.05 probability level was chosen to declare significance.

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

METHODOLOGY (Continued)

Principal statistical methods (continued):

- **Safety**

Cutaneous signs and symptoms (desquamation, dryness, stinging/burning and pruritus) were summarized by worst severity reached. Adverse events were tabulated in frequency tables. Laboratory parameters, vital signs and physical examinations were summarized with descriptive statistics by treatment group.

- **Analyses of Systemic Exposure and Other Assessments**

Systemic exposure data and health questionnaires (DLQI and EQ5D) as well as patient satisfaction data were descriptively summarized.

RESULTS

- **Subject Disposition**

A total of 296 subjects were included and received study treatment.

Summary Table 1 – Subject Disposition

	CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	metronidazole 0.75% BID	vehicle QD	total
ITT population n (%)	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)	296 (100)
Discontinued n (%)	2 (3.9)	2 (4.3)	3 (5.8)	5 (10.4)	4 (8.3)	7 (14)	23 (7.8)
Adverse event	1 (2.0)	2 (4.3)	1 (1.9)	2 (4.2)	2 (4.2)	0	8 (2.7)
Subject's request	0	0	1 (1.9)	1 (2.1)	2 (4.2)	5 (10.0)	9 (3.0)
Protocol violation	1 (2.0)	0	0	1 (2.1)	0	1 (2.0)	3 (1.0)
Lack of efficacy	0	0	1 (1.9)	0	0	1 (2.0)	2 (0.7)
Other reasons	0	0	0	1 (2.1)	0	0	1 (0.3)
Completed the study n (%)	49 (96.1)	45 (95.7)	49 (94.2)	43 (89.6)	44 (91.7)	43 (86)	273 (92.2)
PP population n (%)	48 (94.1)	45 (95.7)	48 (92.3)	43 (89.6)	44 (91.7)	43 (86)	271 (91.6)
Safety population n (%)	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)	296 (100)

Two hundred and seventy three (273, 92.2%) subjects completed the study.

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

RESULTS (Continued)

■ **Demographics and Baseline Data**

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

Summary Table 2 – Demographics and Baseline Data (ITT population)

		CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	metronidazole 0.75% BID	vehicle QD	total
Total	**n (%)**	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)	296 (100)
Gender n (%)	**Female**	31 (60.8)	29 (61.7)	33 (63.5)	39 (81.3)	34 (70.8)	35 (70)	201 (67.9)
	Male	20 (39.2)	18 (38.3)	19 (36.5)	9 (18.8)	14 (29.2)	15 (30)	95 (32.1)
Race n (%)	**Caucasian**	51 (100)	47 (100)	51 (98.1)	48 (100)	48 (100)	50 (100)	295 (99.7)
	Hispanic	0	0	1 (1.92)	0	0	0	1 (0.34)
Age (years)	**Mean±SD**	52.7±13.8	53.4±14.5	50.4±14.5	50.9±12.3	52.2±15.9	52.2±14.4	51.9±14.2
Inflammatory lesions	**Mean±SD**	31.1±15.0	35.1±20.5	35.8±18.2	37.3±39.0	37.4±23.9	35.8±19.9	35.4±23.8
	Median	27.0	29.0	32.5	26.0	31.0	28.5	28.0
	Min/Max	15/79	14/108	16/93	16/270	15/153	15/120	14/270

■ **Efficacy**

After 12 weeks of treatment (ITT-LOCF), the median percent change in inflammatory lesion count was statistically significant different (p 0.014) for both CD5024 1% BID (-78.9%) and QD (-78.3%) versus the vehicle (-60.6%). There was no significant difference versus metronidazole 0.75% BID for any of the CD5024 doses. Results are detailed in Summary Table 3. Results from the PP analysis confirmed these outcomes.

Summary Table 3 – Percent Change of Inflammatory Lesion Count at Week 12 (ITT-LOCF population)

	CD50240 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	metronidazole 0.75% BID	vehicle QD
Total n (%)	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)
Mean ± SD	-65.5± 31.5	-67.5 ± 36.8	-70.0 ± 38.1	-69.2 ± 34.3	-59.9 ± 52.2	-46.5 ± 59.4
Median	-79.3	-76.5	-78.3	-78.9	-69.2	-60.6
Minimum/Maximum	-100/31	-100/79	-100/74	-100/41	-100/212	-100/177
p-value vs. vehicle	0.158	0.061	**0.006**	**0.014**	NA	NA

A dose response relationship at Week 12 was demonstrated throughout a sequential step down analysis starting from CD5024 1% BID down to CD5024 0.1% QD, by removing the highest dose until non-significance was reached.

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

RESULTS (Continued)

■ **Efficacy (continued)**

Results showed a statistically significant dose response down to CD5024 1% QD (p=0.004, ITT LOCF population).

In the ITT population, the distribution of changes from Baseline in Investigator Global Assessment 1 (IGA1) showed a significant difference (p=0.047) between CD5024 1% BID and the vehicle; 54.2% of the subjects had improved by at least two points with CD5024 1% BID, whereas 34% did with the vehicle. The difference was almost statistically significant (p=0.056) for CD5024 1% QD compared to the vehicle. Treatment success with CD5024 at all concentrations was significantly higher (all p 0.036, ITT-LOCF population) compared to the vehicle.

A significant difference was observed for the distribution of changes from Baseline in IGA2 between CD5024 1% both QD and BID and the vehicle (p 0.03, ITT-LOCF population); 53.8% subjects had improved by at least two points with CD5024 1% QD, 56.3% of the subjects had improved with CD5024 1% BID, while only 32% treated with the vehicle had improved. Treatment success with CD5024 1% QD and BID were significantly higher (p<0.05, ITT-LOCF population) than with the vehicle.

Summary Table 4 - Treatment Success at Week 12 (ITT-LOCF population)

	CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1%BID	metronidazole 0.75% BID	vehicle QD
Total n (%)	51 (100)	47 (100)	52 (100)	48 (100)	48 (100)	50 (100)
Investigator Global Assessment score 1						
Success n (%)	32 (62.7)*	30 (63.8)*	34 (65.4)*	34 (70.8)*	30 (62.5)	21 (42)
Investigator Global Assessment score 2						
Success n (%)	34 (66.7)	31 (66)	37 (71.2)*	36 (75)*	31 (64.6)	26 (52)

*p<0.05 versus vehicle

At Week 12-LOCF, the difference in decrease of the erythema scores between any of the CD5024 doses and the vehicle as well as metronidazole 0.75% BID was not statistically significant; mean score changes ranged from -0.7 (vehicle) to -1.0 (CD5024 1% BID). The telangiectasia severity score remained almost unchanged in all treatment groups.

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

RESULTS (Continued)

- **Safety**

The investigator assessment of cutaneous signs and symptoms at Week 12 showed that worsening rates of desquamation, dryness, burning/stinging, and pruritus were similar or lower with CD5024 compared to that of the vehicle or metronidazole 0.75% BID.

Overall, 138/296 subjects reported at least one adverse event. Summary Table 5 below provides an overview of AEs reported during the study.

Summary Table 5 - Overview of Adverse Events (Safety population)

	CD5024 0.1% QD	CD5024 0.3% QD	CD5024 1% QD	CD5024 1% BID	Metronidazole 0.75% BID	vehicle QD
Subjects with at least one AE n (%)	21 (41.2)	23 (48.9)	21 (40.4)	28 (58.3)	19 (39.6)	26 (52.0)
Subjects with related AEs n (%)	5 (9.8)	6 (12.8)	3 (5.8)	7 (14.6)	4 (8.3)	5 (10.0)
Subjects with dermatologic AEs n (%)	8 (15.7)	8 (17.0)	5 (9.6)	7 (14.6)	5 (10.4)	10 (20.0)
Subjects with related dermatologic AEs n (%)	4 (7.8)	5 (10.6)	3 (5.8)	4 (8.3)	3 (6.3)	5 (10.0)
Subjects with SAEs n (%)	1 (2.0)	0	0	2 (4.2)	1 (2.1)	0
Subject discontinuations due to AEs n (%)	1 (2.0)	2 (4.3)	1 (1.9)	2 (4.2)	2 (4.2)	0

Four subjects experienced non-treatment related serious adverse event: collapse secondary to bradycardia, leading to discontinuation (CD5024 0.1% QD), chest pain (CD5024 1% BID), abdominal pain (CD5024 1% BID) and pneumonia (metronidazole 0.75% BID).

Subjects, who received CD5024 1% twice daily experienced twice as much treatment related adverse events than those treated once daily.

Six subjects discontinued the study due to the following treatment related adverse events: irritative dermatitis (CD5024 0.3% QD), watery eyes, burning of the eyes, swelling of mucosa of the nose (CD5024 0.3%QD), facial burning and facial pruritus in the application site (CD5024 1% QD), skin irritation (CD5024 1% BID); flare of rosacea and local irritation (metronidazole 0.75% BID) and burning sensation on the skin (metronidazole 0.75% BID).

No clinically meaningful changes in laboratory test results, vital signs or physical examinations after 12 weeks of treatment were observed in any of the subjects.

NAME OF COMPANY: Galderma	*For regulatory use only*
NAME OR CODE OF FINISHED MEDICINAL PRODUCT: CD5024	
NAME OR CODE OF ACTIVE INGREDIENT(S): CD5024	
EUDRACT/IND No.: 2006-001999-20	
Study Title:	ASSESSMENT OF THE EFFICACY AND SAFETY OF THREE CONCENTRATIONS: 1%, 0.3%, 0.1% OF CD5024 CREAM ONCE DAILY AND CD5024 1% CREAM TWICE DAILY, VERSUS ITS VEHICLE AND VERSUS METRONIDAZOLE (ROZEX®) 0.75% CREAM, IN PATIENTS WITH PAPULOPUSTULAR *ROSACEA* OVER 12 WEEKS

RESULTS (Continued)

- **Systemic Exposure**

Plasma concentrations of CD5024 increased with the doses. The maximum concentration was 6.127 ng/mL and was observed at Week 12 in one subject treated with CD5024 1% cream QD. There was no relationship between the different plasma concentrations of CD5024 and the presence/absence of any adverse event related or not.

- **Other Assessments**

With an increasing dose of CD5024, more subjects agreed that the product had improved "at least somewhat" their *rosacea*. Overall, 68.2% to 84.1% of the subjects in the CD5024 groups were satisfied with the product compared to those treated with the vehicle (46.8%). The patient's quality of life demonstrated a dose related increase of overall quality of life per DLQI.

CONCLUSION

The study demonstrated that in subjects with papulopustular *rosacea* CD5024 1% cream applied once or twice daily was significantly superior to its vehicle for percent change of inflammatory lesion counts, the primary efficacy criterion, as well as for the success rate after 12 Weeks of treatment, confirming a dose relationship.

Overall, erythema had improved with all CD5024 doses; differences versus the vehicle were small and not statistically significant.

Plasma concentration of CD5024 increased with the doses. There was no relationship between the different plasma concentrations of CD5024 and the presence/absence of any adverse event related or not.

The study drug was well tolerated in all treatment groups. No major safety issues were reported and no treatment related serious adverse events or no deaths occurred during the study.