C.P.C.A.D.

STUDY REPORT CR 92140
21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

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06/08/92
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STUDY REPORT CR 92140

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TABLE OF CONTENTS

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

SUMMARY

The aim of the study was to compare the skin irritation potential of gel formulations n°524.635/2 and n°555.089, both containing 0.1% CD 271. For that purpose, twenty five healthy volunteers were enrolled in a 21 day cumulative irritancy open test performed in a double blind, randomized, controlled, intra-individual design. Five days a week (except Saturdays and Sundays), the two gels were applied on two cutaneous sites located on each side of the back without occlusion.

The two gels were well tolerated and the mean cumulative irritancy indexes classified them as being non irritant. Therefore, it is concluded that under the conditions of the test as defined in protocol CR 92140, gels n°524.635/2 and n°555.089 have no clinically significant irritancy potential.

I. INTRODUCTION

The aim of the study was to assess the skin irritation potential of gel n°555.089 compared to that of gel n°524.635/2, both gels including 0.1% CD 271.

CD 271 is a new chemical entity, developed from CIRD GALDERMA research and intended for the topical treatment of acne vulgaris. Previous phase I and clinical studies (reports n° CR 85012 lotion, CR 87016 lotion, CR 87031 lotion, CR 88056 gel, CR 90080 crème) have demonstrated that CD 271 in a lotion, gel (formulation n°524.635/2) or cream formulation has no cutaneous irritancy or sensitization potential.

CD 271 is being developed as an international project. Therefore, gel n°555.089 results from minor changes performed in gel n°524.635/2 in order to meet english and german pharmaceutical authorities requirements. Gel n°555.089 differs from gel n°524.635/2 in the presence of a second preservative, phenoxyethanol, and the replacement of Carbomer 940 at 1% by Carbomer 980 at 1.1%.

II. OBJECTIVE

To assess in healthy volunteers the skin irritancy potential of gel n°555.089 compared to that of gel n°524.635/2, both gels containing CD 271 at 0.1%.

III. STUDY DATES AND SITE

The study was carried out from May 18th, 1992 to June 8th, 1992 at the C.P.C.A.D. (Centre de Pharmacologie Clinique Appliquée à la Dermatologie), Hôpital PASTEUR, 30 avenue de la Voie Romaine, Nice, FRANCE.

IV. MATERIALS AND METHODS

The study was designed, executed and controlled according to the current french Good Clinical Guidelines, except monitoring requirements. Phase I tolerance studies of this type are routinely performed at CPCAD. As other studies of this type have been monitored in the past by CIRD GALDERMA, the sponsor decided that monitoring of this study would not contribute to the quality of the results.

IV.1 Materials

Two test articles were included in the study :

- CD 271 0.1% gel (formulation n°524.635/2, batch n° F8)

- CD 271 0.1% gel (formulation n°555.089, batch n° F1)

Both CD 271 0.1% gels were manufactured and packaged in identical 30 g tubes by GALDERMA Laboratories, 2 avenue de Stalingrad, 92152 CHEVILLY-LARUE. One tube of each gel was archived as a stock sample in CIRD GALDERMA facilities at the beginning of the study. The study containers were returned to CIRD GALDERMA at the end of the study. Post-study analyses confirmed the stability of both CD 271 0.1% gels throughout the study period (see Appendix III).

IV.2 Methods

The skin irritancy test involved 15 applications, five days a week (except on Saturdays and Sundays) during 21 consecutive days. All applications were performed in an double blind manner during the entire duration of the study. Irritation was assessed by the investigator the morning following each day of application (or Monday if the last application was on Friday) and a few minutes later, applications were renewed.

Application sites

The two gels were applied in a random fashion on two cutaneous sites of approximately 5 cm^2 located on each side of the back, one side receiving gel n°524.635/2 and the other side receiving gel n°555.089. The sites were identified using a stencil positioned according anatomical features as a guide and stained with a surgical pen at each visit to assure that the applications were always made on the same cutaneous sites at each visit.

Mode of application

After the subject laid down on his front, 20 µl of each gel material were deposited with a micropipette in the middle of the test zones. Then, materials were spread over the test zones with the rounded end of a glass stirring rod. No occlusion dressing material was used (open-test). After each application, the test zones were air-dried for 10 minutes approximately.

Irritation evaluation

The following grading system was used to evaluate each test site at each reading time :

0.....No erythema
0.5.....Equivocal erythema
1.....Slight erythema, with or without oedema
2.....Moderate erythema, oedema with or without papules
3.....Severe erythema, oedema with or without papules
4.....Severe erythema, oedema with vesicles or blisters

Data analyses

No statistical analysis was required for the evaluation of irritation. Only the Mean Cumulative Irritancy Index (MCII) was computed for each gel material. It is the mean of the sum of the daily irritancy score divided by the number of subjects.

$$MCII = \frac{\text{Total scores from day 1 to day 21 (all subjects)}}{\text{Number of subjects X 15 (number of readings)}}$$

The rules for calculating the above index were :

- should a visit be missed, its score would be that of the previous visit.

- In case of a severe reaction requiring interruption of the application, the maximal score (4) would be attributed to the day after termination of the application and to each day until the end of the study.

- In case of interruption of the application for any other reason, the subject would be excluded from the calculation of the MCII.

The MCII thus calculated was used to classify the different treatment schedules in the following manner :

MCII	IRRITATION CLASSIFICATION
MCII $\leq$ 0.25	NON IRRITANT
0.25 < MCII $\leq$ 1	SLIGHTLY IRRITANT
1 < MCII $\leq$ 2	MODERATELY IRRITANT
2 < MCII $\leq$ 3	SEVERELY IRRITANT
3 < MCII $\leq$ 4	VERY SEVERELY IRRITANT

V. RESULTS

V.1 Population studied

(see table n°1 - Appendix I)

Twenty five consenting healthy volunteers (4 males and 21 females), 18 through 46 years of age were enrolled into the study. All met inclusion and non-inclusion criteria as defined in protocol CR 92140 (Appendix II). All subjects were completely informed as to the materials being tested and what to expect in the study. They all signed an informed consent. No subject dropped out during the course of the study.

All subjects respected the procedures as defined in protocol CR 92140 except subject n° 20 who missed the tenth day application visit. Its score was that of the previous visit, i.e. equal to zero, according to the rules for calculating the mean cumulative irritation indexes as defined in the protocol CR 92140.

Two subjects used some concomitant therapies during the study period. Subject n° 01 experienced a diarrhoea treated with Imodium (loperamide) tablets, three tablets per day, from day -3 to day 0. Subject n°03 took Raniplex (ranitidine) tablets, two tablets per day from day -2 to day 1, and one tablet per day from day 2 to day 4 for a gastritis.

It was considered that these concomitant therapies did not alter the study results and all data for these patients were included in the calculation of the mean cumulative irritation indexes without any restrictions.

V.2 Clinical evaluations

Clinical evaluations and readings were performed by CPCAD nurse except those of days 18 and 21 which were performed by two other trained individuals.

V.2.1 Gel formulation n°524.635/2

(see table n°2 - Appendix I)

No reaction was observed on the test sites where formulation n°524.635/2 was applied, except an equivocal erythema scored 0.5 in subject n°20 at day 8.

V.2.2. Gel formulation n°555.089

(see table n°3 - Appendix I)

No reaction was observed on the test sites where formulation n°555.089 was applied. Moreover, subject n°25 experienced a very slight folliculitis from day 14 to day 21 located at the upper border of the application site. This later manifestation completely disappeared at day 21.

V.3 Mean Cumulative Irritancy Indexes

(see table n°4 - Appendix I)

Calculations of the Mean Cumulative Irritancy Indexes gave the following results :

MATERIALS	M.C.I.I.	CLASSIFICATION
Gel formulation n°524.635/2/F8	0.0013	NON IRRITANT
Gel formulation n°555.089/F1	0.0000	NON IRRITANT

VI. DISCUSSION

Evaluation of the irritation potential of any topical drug is classically based on the calculation of the Mean Irritation Cumulative Index after a 21 day consecutive period of close contact between the material and the skin. For that, an occlusive dressing system allows to maintain this contact between two successive applications.

Formulation n°524.635/2 has been found very well tolerated when applied either under occlusion in a 21 day cumulative test or without occlusion in the following clinical trials. As the respective irritancy potential of formulations n°555.089 and n°524.635/2 were likely to be close, optimization of the irritancy potential assessment by using an occlusive dressing system was not considered as necessary. Therefore, the two gels were applied in a non occlusive manner in the present test.

VII. CONCLUSION

Under the conditions of the test as defined in protocol CR 92140, formulations n°524.635/2 and n°555.089, both containing CD 271 at 0.1%, were very well tolerated and consequently classified as being non irritant.

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

APPENDIX I

TABLES OF RESULTS

TABLE 1

CR92140
DEMOGRAPHICS

subject	Age	Sex
S01	37	F
S02	44	F
S03	46	F
S04	35	F
S05	31	F
S06	46	M
S07	42	F
S08	40	F
S09	29	M
S10	34	F
S11	38	F
S12	43	F
S13	33	F
S14	36	M
S15	31	F
S16	35	F
S17	38	F
S18	27	F
S19	36	F
S20	31	F
S21	32	F
S22	41	F
S23	37	F
S24	43	F
S25	18	M
N	25	25
MEAN	36.1	
MAX	46	
MIN	18	
		F=21
		M=4

Sex : F=FEMALE, M=MALE

TABLE 2

CR92140
SCORE BY SUBJECT AND DAY
(SCORE FROM 0 TO 4)
0.1% CD271 GEL
524635/2/F8

subject	Day 1	Day 2	Day 3	Day 4	Day 7	Day 8	Day 9	Day 10	Day 11	Day 14	Day 15	Day 16	Day 17	Day 18	Day 21
S01	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S02	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S03	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S04	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S06	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S07	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S08	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S09	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S21	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SUM	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEAN	0.000	0.000	0.000	0.000	0.000	0.020	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

SCORE : 0.0=0.0, 0.5=0.5, 1.0=1.0, 2.0=2.0, 3.0=3.0, 4.0=4.0

TABLE 3

CR92140
SCORE BY SUBJECT AND DAY
(SCORE FROM 0 TO 4)
0.1% CD271 GEL
555.089/F1

subject	Day 1	Day 2	Day 3	Day 4	Day 7	Day 8	Day 9	Day 10	Day 11	Day 14	Day 15	Day 16	Day 17	Day 18	Day 21
S01	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S02	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S03	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S04	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S05	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S06	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S07	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S08	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S09	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S11	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S13	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S14	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S15	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S16	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S20	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
S25	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SUM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEAN	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

SCORE : 0.0=0.0, 0.5=0.5, 1.0=1.0, 2.0=2.0, 3.0=3.0, 4.0=4.0

TABLE 4

CR92140
MEAN SCORES OVER DAY 1 TO DAY 21
BY SUBJECT AND PRODUCT

subject	0.1% CD 271	
	555.089/F1	524635/2/F8
S01	0.000	0.000
S02	0.000	0.000
S03	0.000	0.000
S04	0.000	0.000
S05	0.000	0.000
S06	0.000	0.000
S07	0.000	0.000
S08	0.000	0.000
S09	0.000	0.000
S10	0.000	0.000
S11	0.000	0.000
S12	0.000	0.000
S13	0.000	0.000
S14	0.000	0.000
S15	0.000	0.000
S16	0.000	0.000
S17	0.000	0.000
S18	0.000	0.000
S19	0.000	0.000
S20	0.000	0.033
S21	0.000	0.000
S22	0.000	0.000
S23	0.000	0.000
S24	0.000	0.000
S25	0.000	0.000
SUM	0.000	0.033
MEAN	0.0000	0.0013

Mean : Mean Cumulative Irritancy Index (M.C.I.I.)

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

APPENDIX II

PROTOCOL N° CR 92140

This document is an English language translation of the original French language version of pages 1 to 22 of protocol CR 92140.

Translation verified by : Dr. C. RAYBAUT, Study Investigator

CRay 06/08/92

Signature **Date**

COPY OF THE FRENCH APPROVAL SHEET

C.P.C.A.D. **PROTOCOLE D'ESSAI CHEZ L'HOMME**

PROMOTEUR : CIRD GALDERMA SOPHIA ANTIPOLIS 06565 VALBONNE	**PROTOCOLE N° :** CR92140
TITRE DU PROTOCOLE : TEST D'EVALUATION DE LA TOLERANCE CUTANEE APRES APPLICATION ITERATIVE DE 21 JOURS EN PEAU SAINE DE DEUX FORMULATIONS GEL DU CD 271 A 0.1 %	
PROJET : CD 271 gel	**PRODUIT A TESTER :** - CD 271 à 0.1 % (555.089) - CD 271 à 0.1 % (524.635/2)
DATES DE L'ESSAI : MAI/JUIN 1992	**LIEU DE L'ESSAI :** CPCAD HOPITAL PASTEUR -NICE

APPROBATIONS

POUR LE CPCAD :

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Pr. H. SCHAEFER, Président, 10/06/92

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Dr. M. VERSCHOORE, Moniteur, 19 05 92

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- **dossier de l'étude (original)**
- **aux personnes responsables ci-dessus**
- **aux personnes concernées ci-après :**

C. D'AUTHIER / C. PERNIN

C.P.C.A.D. HUMAN STUDY PROTOCOL

SPONSOR : CIRD GALDERMA SOPHIA ANTIPOLIS 06565 VALBONNE	**PROTOCOL N° :** CR 92140
PROTOCOL TITLE : 21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0,1 % CD 271 GEL FORMULATIONS	
PROJECT : CD 271	**TEST ARTICLES :** -- 0,1 % CD 271 gle n° 555.089 - 0.1 % CD 271 gel n° 524.635/2
TEST DATES : MAY/JUNE 1992	**STUDY CENTRE :** CPCAD HOPITAL PASTEUR -NICE

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FOR CPCAD :

Dr. C. RAYBAUT, Investigator

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Pr. J.P. ORTONNE, Director

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FOR THE SPONSOR :

J.P. BILLOT, Development Manager

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Dr. J. CZERNIELEWSKI, Clinical Research Department Head

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N. KAIL, Quality Manager

_____/__/__/__/

Dr. M. VERSCHOORE, Monitor

_____/__/__/__/

PROTOCOLE DISTRIBUTION :

- **study file (original)**
- **to the above supervisors**
- **to the following :**

C. PERNIN / C. D'AUTHIER

I. INTRODUCTION

CD 271 is a new chemical entity developed from CIRD GALDERMA research. It is a naphtoic acid derivative, assimilated to the retinoids, and designed as a topical treatment of acne. This compound has been clinically tested in Phases I, II and III in approximately one thousand subjects. Its safety and efficacy have been found satisfactory.

Clinical studies PC 85013/2, CR 88056 and CR 90080 have shown that CD 271 formulated in a lotion, a gel (formulation n°524.635/2 including 0.1% CD 271) or a cream has no irritancy potential for human skin. This has been confirmed in further phase 2 and 3 clinical studies performed in acneic patients. No case of sensitization to any of these three formulations has been reported to date.

Gel n°555.089 results from minor changes in gel n°524.635/2 in order to meet english and germain pharmaceutical authorities requirements (CD 271 is being developed as an international project). Gel n°555.089 differs from gel n°524.635/2 in the presence of a second preservative, phenoxyethanol, and the replacement of Carbomer 940 at 1% by Carbomer 980 at 1.1%.

The aim of the study was to assess the skin irritation potential of gel n°555.089 compared to that of gel n°524.635/2, both gels including 0.1% CD 271. For that purpose, a skin irritation assessment after repeated applications will be carried out using a method derived from that described by Philips et al. (ref.1).

II. STUDY PURPOSE

To assess in healthy volunteers the skin irritancy potential of gel n°555.089 compared to that of gel n°524.635/2, both gels including CD 271 at 0.1%, after a 21 day cumulative irritancy period.

III. STUDY DATES AND SITE

The 21-day study will be conducted in the C.P.C.A.D. (Centre de Pharmacologie Clinique Appliquée à la Dermatologie), Hôpital PASTEUR, 30 avenue de la Voie Romaine, Nice, FRANCE.

IV. STUDY DESIGN

Controlled, randomised, double-blind, crossover study.

V. STUDY POPULATION

V.1. Inclusion criteria

. 25 subjects (healthy volunteers) of either sex, aged between 18 and 50 years.

. Females who have been using effective means of contraception for at least three months before the beginning of the study and who continue to do so throughout the study and for one month completion. The patient will be asked to confirm verbally that she is not pregnant at the time of inclusion and this will be recorded on the case report forms.

. Subjects who can be monitored as out-patients.

. Subjects informed of the aim and procedure of the study and who have signed the informed consent form.

. Subjects having passed a clinical examination certifying their suitability for taking part in the study.

. Subjects covered by a Health Insurance scheme.

V.2. Exclusion criteria

. Subjects suffering from a skin disorder in the test zone (back), which could adversely affect the clinical assessment.

. Subjects using topical or systemic treatment which could interfere with the test results (as judged by the clinician).

. Pregnant women or lactating mothers.

. Subjects with a known allergy to one of the ingredients of the test articles or to the occlusive dressing material.

. Subjects who have participated in a pharmacological test within the three months preceding the trial.

V.3. Drop-out criteria

. Any subject requiring, in the course of the study, a therapy which could interfere with the test results. In this case, the subject is required to inform the clinician who will record the event on the case report form and decide if the study may be continued or not.

. Non compliance with the protocol prejudicial to the validity of the results.

Any drop-out is to be fully documented by the investigator on the case report form "Final report" (see section "Drop- outs").

Any unexpected Adverse event is to be fully documented by the clinician on the case report form "Adverse event" (see section "Adverse event").

VI. MATERIALS AND METHODS

VI.1. Test articles

- CD 271 0.1% gel (formulation n°524.635/2)

- CD 271 0.1% gel (formulation n°555.089/F1)

Both CD 271 0.1% gels will be manufactured by GALDERMA Laboratories, 2 avenue de Stalingrad, 92152 CHEVILLY-LARUE and supplied to the investigator before the start of the study. Both gels will be packaged in identical 30g tubes identified by a code letter "A" or "B" according to the test material. Allocation of the code letters to the test materials will be kept by an individual who is not the investigator.

The sponsor is responsible for providing the investigator with :

- An appropriate pre-clinical informational brochure on the test materials
- A description of each test material provided by the manufacturer.
- An analytical certificate for each test material.

The monitor or sponsor may request a post-study check if he considerers it necessary. A stock sample of each test material will be taken at the beginning of the study and archived at the C.P.C.A.D.

VI.2. Methods

The method used will be based in that described by Philips et al. (1). It is a skin irritation test without occlusion (open-test)
Throughout the trial period, all the patients will be examined by the same clinician, or the same person trained by him, who will carry out the applications and readings. In addition, he will record the results of the readings and any comments made by the subject, on the appropriate case report forms.

VI.2.1. Application zones

The test articles (n=2) will be applied on two quadrangular zones approximately 5 cm^2, i.e. 2.24 x 2.24, located to the upper part of the back (either side of the spine) using a stencil positioned using anatomical features as a guide. The test articles will be applied on the same sites throughout the study period.

VI.2.2. Application methodology

Each subject will receive a serial number (study admission number) corresponding to a randomized sequence of application of the test articles. The zones tested will be identified by the numbers 1 and 2, allocated as shown on the following plan :

spine
I
Left side 1 I 2 Right side
I

VI.2.3 Schedule

The method involves 21 days of applications of the test articles, 5 days a week (not the week-end), for three consecutive weeks.

Scoring of the skin reaction (cf. section VI.2.5. below: Scoring System), will be carried out on each site the day following each application (or on a monday if the previous application was on friday) and before the next application (i.e. a total of 15 readings).
The study must start on a monday. The study schedule is as follows :

Week 1 :	MONDAY (D0)	)	application
	TUESDAY	)	
	WEDNESDAY	)	scoring
	THURSDAY	)	application
	FRIDAY	)	
	SATURDAY	)	no scoring
	SUNDAY	)	no application
Week 2 :	MONDAY (D7)	)	
	TUESDAY	)	
	WEDNESDAY	)	scoring
	THURSDAY	)	application
	FRIDAY	)	
	SATURDAY	)	no scoring
	SUNDAY	)	no application
Week 3 :	MONDAY (D14)	)	
	TUESDAY	)	
	WEDNESDAY	)	scoring
	THURSDAY	)	application
	FRIDAY	)	
	SATURDAY	)	no scoring
	SUNDAY	)	no application
Week 4 :	MONDAY (D21)	)	scoring

VI.2.4. Mode of application :

The test articles will be applied to the subject's back with the subject lying on his front. 20 µl of each gel will be placed on the corresponding test zone using an Eppendorf micropipette. The gel will then be spread over the test zone and massaged until surface excess has disappeared (approximately 20 seconds). After application, the test zones will be allowed to air-dry for approximately 10 minutes.

VI.2.5. Scoring system

The skin reaction will be scored according to the following scale :

0.....No erythema
0.5.....Equivocal erythema
1.....Slight erythema, with or without oedema
2.....Moderate erythema, oedema with or without papules
3.....Severe erythema, oedema with or without papules
4.....Severe erythema, oedema with vesicles or blisters

As the test will be repeated on the same sites for 21 consecutive days (i.e. a total of 15 applications), if there is an excessively severe reaction on one or several sites, application of the causative test article(s) will be stopped on that (those) site(s).

An excessively severe reaction is defined as follows:

. reaction >= 3
. and/or unbearable discomfort reported by the subject,
. and/or according to the clinician's personal opinion, which must be justified.

The clinician, or a person trained by him, will record on the case report form the day that application was stopped for the test article(s) concerned and the score attributed at the time that it was stopped.

In case of a severe and persistent reaction, it is the responsibility of the clinician to provide medical treatment and follow-up for the subject.

All cases where the application of a test article(s) is stopped for a reason other than a severe reaction will be recorded by the clinician in the case report form.

VII. DROP-OUTS AND LOST TO FOLLOW-UP

VII.1. Drop-outs

Premature terminations will be requested when decided by the investigator for safety reasons (i.e. when severe skin reaction occurs, when concomitant therapy is not allowed, when a female patient becomes pregnant,etc...). Premature terminations may also be requested by the patient. In all cases, cessation of treatment must be carefully documented by the investigator using the Final Report form and, if need be, the Adverse Event forms.

VII.2 Lost to follow-up

In case a patient does not appear for the visit, the investigator will try twice to reach him by phone and will then send him a letter before considering him/her lost to follow-up. This will be documented on the final report form.

VIII. ADVERSE EVENTS

All adverse events occurring during this study must be reported on the forms provided. A separate Adverse Event form must be completed for each event for each patient. This form must be returned to the sponsor within the time frames defined below.

VIII.1 Non serious Adverse Event

A non serious adverse event is defined as occurrance of new symptoms of a medical nature during use of the test article. Any event requiring medical/surgical intervention should be reported, e.g. influenza, broken bones, fever, nausea, etc.. These events must be reported on the Adverse Event form which will be kept in the corresponding subject's booklet. The outcome of the adversde event must be also reported in the Adverse Event form.

VIII.2 Serious Adverse Event

Serious adverse events are defined as any finding which suggests a significant hazard, contraindication, side effect, or precaution. Additionally, any adverse event which results in a fatality, is life threatening or is permanently disabling, requires in-patient

hospitalization, prolongs a current hospitalization, is a congenital anomaly, cancer, or overdose is also considered a serious adverse event.

Serious adverse events must be reported to one of the following individuals within 24 hours of the investigator's knowledge of the event:

J. CZERNIELEWSKI	CPCAD DIRECTOR	Tel : 93957070
C. RAYBAUT	CPCAD M.D.	Tel : 93957070

An Adverse Event Form should be completed for all serious adverse events and forwarded to the sponsor within 24 hours. Follow-up Adverse Event Forms should be filled out and forwarded to the sponsor when new significant information is obtained as well as when outcome of the event is known. Depending on the nature and seriousness of the adverse event, copies of the medical record of the patient may be requested as well as results of laboratory tests performed. If the patient was hospitalized, a copy of the discharge summary may be forwarded to the sponsor as soon as it is ready. In certain cases, a letter from the investigator summarizing events related to the case may be requested. In all instances, investigators should follow patients until an outcome to the event is known.

VIII.3 Patch test

In the event that any patient develops an unusually severe degree of erythema/irritation that is suspected to be treatment related and possibly a case of contact or allergic contact dermatitis, that patient should be patch tested with both gel formulations coded "A" and "B". Patches will be applied to the back for 48 hours. Reading will be performed one hour after patch removal. The patch test sites will also be read at 96 hours.

The following grading system will be used for reading patch test sites :

0	NO DERMATITIS
0.5	EQUIVOCAL DERMATITIS NOT COVERING THE TEST SITE
1	ERYTHEMA COVERING THE TEST SITE
2	ERYTHEMA AND INDURATION COVERING THE TEST SITE
3	ERYTHEMA, INDURATION AND VESICLES COVERING THE TEST SITE
4	ERYTHEMA, INDURATION VESICLES AND BULLA(E) COVERING THE TEST SITE

A separate Patch Test Form will be used to document all patch test results. If tolerance is unacceptable, the patient will terminate the treatment, a final report form will be filled and an Adverse Event form completed.

IX. CONCOMITANT THERAPIES

No medication, other than the study medication, is permitted. Especially, retinoids are to be avoided. Patients undergoing therapies interfering with the tested medications (as judged by the clinicien) during the trial will be excluded from the analysis. Information (name,composition, dosage regimen, dates of initiation and of termination) on concomitant medication, should be recorded in the "Concomitant medications" form.

X. RESULTS ANALYSIS

In order to compare scores, a Mean Cumulative Irritation Index (M.C.I.I.) will be calculated for each gel. The M.I.I. is the sum of the scores of the fifteen readings, divided by the number of subjects included in the study and the number of readings (15) (max. M.I.I. = 4).

$$\text{M.I.I.} = \frac{\text{Sum scores of the 15 readings (all subjects)}}{\text{Number of subjects x 15 (readings)}}$$

The rules when calculating this index are :

- If a subject misses an examination, the reading on the day of absence will be the same as the preceding day's score.

- If application is stopped because of a severe reaction, the maximum score (4) will be attributed on the day following discontinuation of application of the gel on the site concerned and this score will be attributed until the end of the irritation test.

- If an application is stopped for another reason, the subject's scores will be excluded from the calculation of the indices.

The M.C.I.I. values obtained will be compared and the two gel formulations will be classified according to the following scale :

MCII	IRRITATION CLASSIFICATION
MCII $\leq$ 0.25	NON IRRITANT
0.25 < MCII $\leq$ 1	SLIGHTLY IRRITANT
1 < MCII $\leq$ 2	MODERATELY IRRITANT
2 < MCII $\leq$ 3	SEVERELY IRRITANT
3 < MCII $\leq$ 4	VERY SEVERELY IRRITANT

IX. REGULATORY ARRANGEMENTS

IX.1 Regulatory procedures

This study will be carried out in accordance with law n° 88-1138 ("Huriet") dated 20 december 1988 and its enforcement orders concerning the protection of persons who participate in biomedical research and in accordance with the Good Clinical Practices defined in the "Bulletin Officiel" published by The French Ministry of Social Services and Employment. This study will be declared to the French Health Ministry and the Director of the Hôpital Pasteur, Nice (France) will be informed of the conduct of the study in his hospital.

IX.2. Ethics Committee

This protocol will be submitted to the "Comité Consultatif de Protection des Personnes du C.H.R. de Nice" for their opinion in accordance with regulatory requirements.

IX.3. Research Centre Authorisation

A request for registration of the C.P.C.A.D. as a research centre with no direct individual profit, has been submitted. A tacit agreement has been obtained.

IX.4. Informed consent

All volunteers taking part in this trial will have been fully informed about the study in accordance with the HELSINKI declaration (1964) and the TOKYO (1975), VENICE (1983) and HONG-KONG (1989) amendments and in accordance with the "Huriet" law (1988). Duplicate copies of the informed consent forms will be signed by the volunteers. One copy will be archived with the study report and the volunteer will retain the other copy.

IX.5. Monitoring

The conduct of the study will be verified by the appointed monitor. The reports of these checks will be also archived with the study report.

IX.6. Test article handling

The pharmacist at the Hôpital Pasteur, Nice will be informed of the study. In agreement with the pharmacist at the Hôpital Pasteur, Nice, the investigator will be responsible for the storage, supply and inventory of the samples which will be returned to the sponsor at the end of the study. A stock sample of each test article will be archived with the study documentation.

IX.7. Insurance

A certificate attesting Third Party coverage of CIRD GALDERMA is appended to this protocol.

IX.8. Quality assurance

This study will be audited by our Quality Assurance Department and an audit certificate will be appended to the final report.

IX.9. Archives

The protocol, raw data, report, correspondence, a sample of each test article and all other material relating to the study (e.g. any photographs and specimens, contract, amendments etc.) will be archived for 15 years in C.P.C.A.D. files.

IX.10. Contractual requirements

An contractual agreement will be signed by the sponsor and the investigator. This document will contain complementary information, i.e. financial agreement, confidentiality, study schedule, third party responsability, and publication of study results.

BIBLIOGRAPHIC REFERENCES

(1) PHILIPS, STEINBERG M., MAIBACH H.I., AKERS W.A.
A comparison of rabbit and human skin responses to certain irritants. Toxicol. Applic. Pharmacol 21 : 369, 1972

SELECTION CRITERIA

(mark the appropriate box)*

	YES*	NO*
. Subject aged over 18 or less than 50 years	/__/	/__/
. Female who has been using effective contraception for at least three months before the beginning of the test	/__/	/__/
. Subject has signed the informed consent form	/__/	/__/
. Subject is covered by a Health Insurance scheme	/__/	/__/
. Subject has passed a clinical examination showing his suitability for taking part in this study	/__/	/__/

TO INCLUDE THE SUBJECT, ALL ANSWERS MUST BE YES

. Subject with a skin disorder on the test zone which could affect clinical assessment	/__/	/__/
. Subject receiving or having received local or systemic treatment which could interfere with the test results	/__/	/__/
. Subject for whom one of the ingredients of the test articles is contra-indicated	/__/	/__/
. Pregnant females or lactating mothers	/__/	/__/
. Subject having taken part in a pharmacological test in the 3 months preceding the trial	/__/	/__/

TO INCLUDE THE SUBJECT, ALL ANSWERS MUST BE NO

Subject included in the study ? /___/yes /___/no

If yes, TRIAL INCLUSION NUMBER (SUBJECT N°) : /__/__/

DATE : /___/___/___/
DD MM YY

CLINICIAN'S SIGNATURE :

SUBJECT'S INITIALES /__/__/__/ /__/ **SUBJECT N° :** /__/__/

CASE REPORT FORM

SITES DATES	1 paravertébral left	2 paravertébral right	COMMENTS	SIGNATURES
TUESDAY/J1 Date:				
WEDNESDAY/D2 Date :				
THURSDAY/D3 Date :				
FIRDAY/D4 Date :				

REACTION SCORING SYSTEM

0.....No erythema
0.5.....Equivocal erythema
1.....Slight erythema, with or without oedema
2.....Moderate erythema, oedema with or without papules
3.....Severe erythema, oedema with or without papules
4.....Severe erythema, oedema with vesicles or blisters

ADVERSE EVENT ? /__/yes /__/no
If yes, fill out the Adverse event forms

CONCOMITANT THERAPY ? /__/yes /__/no
If yes, fill out the Concomitant medications form :

COMMENTS : _____

_____

DATE : /___/___/___/ INVESTIGATOR'S SIGNATURE :

SUBJECT'S INITIALES /__/__/__/ /__/ **SUBJECT N° :** /__/__/

CASE REPORT FORM

SITES DATES	1 paravertébral left	2 paravertébral right	COMMENTS	SIGNATURES
MONDAY/D7 Date :				
TUESDAY/D8 Date:				
WEDNESDAY/D9 Date :				
THURSDAY/D10 Date :				
FRIDAY/D11 Date :				

REACTION SCORING SYSTEM

0.....No erythema
0.5.....Equivocal erythema
1.....Slight erythema, with or without oedema
2.....Moderate erythema, oedema with or without papules
3.....Severe erythema, oedema with or without papules
4.....Severe erythema, oedema with vesicles or blisters

ADVERSE EVENT ? /__/yes /__/no
If yes, fill out the Adverse event forms

CONCOMITANT THERAPY ? /__/yes /__/no
If yes, fill out the Concomitant medications form :

COMMENTS : _____

_____

DATE : /___/___/___/ INVESTIGATOR'S SIGNATURE :

SUBJECT'S INITIALES /__/__/__/ /__/ **SUBJECT N° :** /__/__/

CASE REPORT FORM

SITES DATES	1 paravertébral left	2 paravertébral right	COMMENTS	SIGNATURES
MONDAY/D14 Date :				
TUESDAY/D15 Date:				
WEDNESDAY/D16 Date :				
THURSDAY/D17 Date :				
FRIDAY/D18 Date :				
MONDAY/D21 Date :				

REACTION SCORING SYSTEM

0.....No erythema
0.5.....Equivocal erythema
1.....Slight erythema, with or without oedema
2.....Moderate erythema, oedema with or without papules
3.....Severe erythema, oedema with or without papules
4.....Severe erythema, oedema with vesicles or blisters

ADVERSE EVENT ? /__/yes /__/no
If yes, fill out the Adverse event forms

CONCOMITANT THERAPY ? /__/yes /__/no
If yes, fill out the Concomitant medications form :

COMMENTS : _____

_____

DATE : /___/___/___/ INVESTIGATOR'S SIGNATURE :

SUBJECT'S INITIALES /__/__/__/__/ **SUBJECT N° : /__/__/**

FINAL REPORT

DATE OF LAST APPLICATION /___/___/___/
DD MM YY

Reason for termination

Normal completion	1	Non compliance	6
Adverse event	2	Pregnancy	7
Concomitant therapy	3	Other	9
Lost-to-follow-up	4*	_____	
		_____	

*Date of 1st call /___/___/___/
DD MM YY

*Date of 2nd call /___/___/___/
DD MM YY

*Date of letter /___/___/___/
DD MM YY

Investigator's comments_____
_____
_____

Subject's comments : _____
_____

Date : /____/____/____/
DD MM YY

Investigator's signature :

SUBJECT'S INITIALES /__/__/__/__/ **SUBJECT N° : /__/__/**

CONCOMITANT MEDICATIONS FORM

COMMERCIAL NAME	REGIMEN	DATE START	DATE STOP	REASON*

* fill out the Adverse event forms for any Adverse event

Comments_____
_____
_____

Date : /___/___/___/ **Investigator's signature :**
DD MM YY

SUBJECT'S INITIALES /__/__/__/ /__/ **SUBJECT N° : /__/__/**

Test medication used : _____

ADVERSE EVENT FORM

A. Description of adverse event (one event per form)

_____

_____

B. Was event serious ? /__/ 1 Non /__/ 2 Oui

C. Date of event onset /___/___/___/
DD MM YY

D. Has this event previously been reported by this patient ?
(Explain in comment section)
/__/ 1 Non
/__/ 2 Yes, before the start of the study
/__/ 3 Yes, intermittently
/__/ 4 Yes, chronic medical event

E. How soon after study drug application did event occur ?
/__/ 1 Upon application
/__/ 2 Within 1 hour of application
/__/ 3 Within 24 hours of application

F. Duration of event
(fill in number 1 and check unit if event has resolved)
/__/ 1 Duration _____
/__/ 2 Not applicable

G. Severity of event
/__/ 1 Mild
/__/ 2 Moderate
/__/ 3 Severe

H. Action taken (Check all that reply, explain in comment section)
/__/ 1 None
/__/ 2 Reduce frequency of application
/__/ 3 Discontinued drug temporarily
/__/ 4 Discontinued drug permanently /___/___/___/
DD MM YY
/__/ 5 Hospitalized patient from /__/__/__/ to /__/__/__/
DD MM YY DD MM YY
/__/ 6 Prolonged a current Hospitalization
/__/ 7 Other_____

I. Outcome of event
/__/ 1-Resolved without treatment /___/___/___/
DD MM YY
/__/ 2-Resolved with treatment /___/___/___/
DD MM YY
/__/ 3-Continuing without treatmentt
/__/ 4 Continuing with treatment (explain in comment section)
/__/ 5-Patient lost to follow-up, no further detail available
/__/ 6-Patient died /___/___/___/
DD MM YY
List cause of death in comment section

J. Patch test performed ? /__/ 1 No /___/ 2 Yes

K. If yes, was there a positive response ?
(Explain in comment section)
/__/ 1 No /__/ 2 Yes 3 /__/ Equivocal

L. Relationship of event to study drug (see manual of definition) ?
/__/ 1 Definititely unrelated /__/ 4 Probable
/__/ 2 Unlikely /__/ 5 Definitely related
/__/ 3 Possible

M. Possible explanation (s) for event (check all that apply : . Explain in comment section)
/__/ 1 Illness being treated
/__/ 2 Intercurrent illness
/__/ 3 Study drug
/__/ 4 Non study drug
/__/ 5 Drug interaction
/__/ 6 Other

N. For masked study only :
Has the code been broken for this patient ?
/__/ 1 No /__/ 2 Yes

Complete the Adverse event narrative report form if necessary (following page)

Comments : _____

_____

Date : /___/___/___/
DD MM YY

Investigator's signature :

Mail this form completed within 24 hours in case of serious Adverse event

SUBJECT'S INITIALES /__/__/__//__/ **SUBJECT N° : /__/__/**

ADVERSE EVENT NARRATIVE REPORT FORM

Date : /___/___/___/
DD MM YY

Investigator's signature :

DEFINITION OF TERMS
ADVERSE EVENT FORM

The Adverse Event form should be completed within 24 hours of any medical event and mailed to the sponsor upon completion.

B. **Was the Adverse Event Serious :**
1 - No
2 - Yes, Serious is defined as any experience suggesting a significant hazard, contra indication, side effect or precaution and includes any experience that is fatal, life threatening, permanently disabling, requires inpatient hospitalization, or congenital anomaly, cancer or overdose. The definitions for life threatening, permanently disabling and inpatient hospitalization are below :
Life threatening - immediate risk of death from reaction as it occured.
Permanently disabling - permanent and substantial disruption of one's ability to carry out normal life functions.
Inpatient hospitalization - includes prolongation of existing hospitalization.

FOR QUESTIONS :

G. **Intensity of Adverse Event :**
1 - *Mild* - awareness of sign or symptom, but easily tolerated
2 - *Moderate* - discomfort enough to cause interference with usual activity
3 - *Severe* - incapacitating with inability to work or to perform usual activity

M. **Relationship of event to study drug ?**
1.- *Definitely unrelated* - Should be reserved for those events which occur prior to test drug administration (i.e. washout or single-blind placebo) or those events which cannot be even remotely related to study participation (i.e., injuries sustained in an automobile accident).

2 - *Unlikely* - There is no reasonable temporal association between the study drug and the suspected event and the event could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

3.- *Possible* - the suspected adverse event may or may not follow a reasonable temporal sequence from study drug administration but seems to be the type of reaction that cannot be dismissed as unlikely. The event could have been produced or mimicked by the patient's clinical state or by other modes or therapy concomitantly administered to the patient.

4.- *Probable* - The suspected adverse event follows a reasonable temporal sequence from study drug administration, abates upon discontinuation of the drug, and cannot be reasonably explained by the known characteristics of the patient's clinical state.

5.- *Definitely related* - Should be reserved for those events which have no uncertainty in their relationship to test drug administration (i.e. Positive Rechallenge).

SUBJECT'S INITIALS /__/__/__//__/ **SUBJECT N° : /__/__/**

PATCH TEST FORM
(circle the answer)

Date of application /_____/_____/_____/
DD MM YY

Application site Arm /___/
Back /___/

upper to lower site	**48 H reading** Date /___/___/___/ DD MM YY RESULTS	**96 H reading** Date /___/___/___/ DD MM YY RESULTS
GEL A	0 0.5 1 2 3 4	0 0.5 1 2 3 4
GEL B	0 0.5 1 2 3 4	0 0.5 1 2 3 4

Score by using the following scale :

0 NO DERMATITIS
0.5 EQUIVOCAL DERMATITIS NOT COVERING THE TEST SITE
1 ERYTHEMA COVERING THE TEST SITE
2 ERYTHEMA AND INDURATION COVERING THE TEST SITE
3 ERYTHEMA, INDURATION AND VESICLES COVERING THE TEST SITE
4 ERYTHEMA, INDURATION VESICLES AND BULLA(E) COVERING THE TEST SITE

Date : /___/___/___/ **Investigator's signature**
JJ MM YY

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

SUBJECT INFORMATION - INFORMED CONSENT

The purpose of this study is to ensure that two gel formulations containing 0.1% CD 271 (product issued from CIRD GALDERMA research and currently under developement) have no irritancy potential for human skin.

This test will be carried out as follows :

For three consecutive weeks, two gel formulations will be applied to your back, on 2 zones approximately 5 cm2 in size, 5 days a week (not saturday and sunday) during 21 consecutive days. The day following each application (or monday if the last application was on friday), the doctor will check your back and the application will then be renewed. You will come back on monday of the 4th week for the last check.

These repeated applications may produce a skin irritation with moderate redness and possibly burning or pruritus on the application sites. These manifestations will dispear spontaneously in a few days. In case of marked irritation, applications will be interrupted. You will be asked not to dampen and/or wash the application sites during the 21 day study period.

This test will be carried out in a hospital, under medical supervision.

The subject who agrees to take part in this test is free to stop at any time if he/she so desires. He/she must comply with the following restrictions :

- to avoid intense physical exercise during the hours preceeding the study;
- not to take any medicines during the test without informing the doctor ;
- to keep the appointments punctually ;

STATEMENT OF CONSENT

After having read the above, I declare :

1. That I have been informed of the nature of the research project and its purpose in conformity with the Helsinki declaration (1964) and the Tokyo (1975), Venice (1983) and Hong Kong (1989) amendments.

2. That I have noted that this study will be conducted in conformity with law n° 88-1138 ("Huriet") dated 20 december 1988 concerning the protection of persons who participate in biomedical research, and also in accordance with the Good Clinical Practices defined in the "Bulletin Officiel" published by the French Ministry of Social Services and Employment.

3. That I have noted that this study has been approved by the "Comité Consultatif de Protection des Personnes du C.H.R. de Nice".

4. That I had a medical examination before being included in this study.

5. That I understand that I may withdraw from this study at any time without prejudice of any sort.

6. That I have noted the names and telephone numbers of the study doctor and nurse :

Doctor C. RAYBAUT	telephone :	93 81 75 18 (CPCAD) 93 84 56 97 (Home)
C. D'AUTHIER	telephone :	93 81 75 18 (CPCAD)

7. That I have not taken part in any other biomedical research in the 3 months preceding this test.

8. That I agree to refrain from participating in another clinical test for three months following this one.

9. That I have been informed that C.P.C.A.D. and the study sponsor are insured for third party risks by the GAN Insurance Company, 44 rue de Châteaudun, 75448 Paris.

10. That I am currently covered by a Health Insurance scheme.

11. For females, certify that I am not pregnant or breast feeding. That I have been using a safe method of contraception throughout the three months preceding the start of the study, and that I will continue this contraception for the period of the study and for one month thereafter.

12. That I have noted that all personal information concerning myself will be archived in a computerised data base but will remain strictly confidential and that I have right of access and rectification (art. 27 of the statute dated January 6th, 1978 on electronic data processing and freedom of information).

13. That I have been informed that certain personal details (i.e. the first three letters of my surname, the first two letters of my Christian name, my date of birth, the date of my entry into the study and that of my termination, the date on which the restrictions concerning my entry into another study expire, and the sum I receive for expenses and compensation for inconvenience) will be recorded in a computerised national centre (art. R2046- Decree No. 90-872 of the Hurier act).

14. That I have been informed that I shall receive the sum of 2500 francs for expenses and compensation for inconvenience.

15. That I have been informed of the fact that the CPCAD has requested, from the DRASS in Marseille, the right to become a "Research Centre dispensing no direct individual benefits" , and that tacit approval has been given.

16. That I have been informed that it is obligatory for me to carry on my person a copy of the Informed Consent Form throughout the duration of the study.

SUBJECT N°

Date and signature of
the investigator

At Nice, (date)

Prepared in duplicate,
one copy for the volunteer
Date and signature of
the volunteer
(preceded by the statement
"read and approved")
At Nice (date)

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

APPENDIX III

ANALYTICAL CERTIFICATES AND POST STUDY CONTROL

ANALYTICAL CERTIFICATE

PRODUCT: **CD 271 GEL AT 0.1%**

LOT NUMBER: 555089/F1

MANUFACTURING DATE: 20.02.1992

ANALYSIS NUMBER: **DA W 533**

PACKAGING: LDPE tubes C20 (30g)

ANALYSIS DATE: 02.03.1992

PACKAGING DATE: 21.02.1992

ANALYTICAL METHODS	STANDARDS	RESULTS
CHARACTERISTICS		
Appearance	white gel	Conforms
Microscopic observation	fine, even dispersion 90% of particles < 10 µm 95% of particles < 20 µm 99% of particles < 80 µm	Conforms
IDENTIFICATIONS		
CD 271 (HPLC)	Rt conforms with the standard	Conforms
Methyl parahydroxybenzoate (HPLC)	Rt conforms with the standard	Conforms
Phenoxyethanol (HPLC)	Rt conforms with the standard	Conforms
Sodium edetate (colorimetry)	Characteristic colour	Conforms
TESTS		
pH	about 5	5.00
Viscosity		
Brookfield Needle TC-Speed 5-25°C	to be defined	64 10^3 cPs
Microbiological assay		
• Total bacterium	< 5 10^2 germs/g	Conforms
• Yeasts and moulds	< 5 10^2 germs/g	Conforms
• Pathogenic bacterium	absence	absence
Mean weight	tubes filled with 30 g	30.17 g

ASSAYS

		Start	Middle	End
CD 271 (HPLC)	0.095 - 0.105%	0.100%	0.100%	0.099%
Methyl parahydroxybenzoate (HPLC)	0.09 - 0.11%	0.102%	0.100%	0.102%
Phenoxyethanol (HPLC)	0.225 - 0.275%	0.250%	0.247%	0.249%
Sodium edetate (limit assay)	about 0.1%	Conforms		

CONCLUSION

The product conforms to the specifications and was accepted.

Analysis methods: European pharmacopoeia + 88151 + 91510.

HEAD
ANALYTICAL SERVICE

RESPONSIBLE
PHARMACIST

ANALYTICAL CERTIFICATE

PRODUCT: **CD 271 GEL AT 0.1%**

LOT NUMBER: 524635/2/F8

MANUFACTURING DATE: 17/08/1990

ANALYSIS NUMBER: **DA U 347**

PACKAGING: LDPE tubes C20 (30g)

ANALYSIS DATE: 23/08/1990

ANALYTICAL METHODS	STANDARDS		RESULTS
CHARACTERISTICS			
Aspect	White gel		Conforms
Microscopic observation	Fine, even dispersion 90% of particles < 20 µm No agglomerates > 80 µm		Conforms
IDENTIFICATIONS			
CD 271 (HPLC)	Rt conforms with the standard		Conforms
TESTS			
pH	About 5		5.10
Viscosity Brookfield Needle TC-Speed 5-25°C	To be defined		70 10^3 cPs
Mean weight	28.5 - 31.5 g		30.33 g
Microbiological assay	< 5 10^2 germs/ml		Conforms
ASSAYS			
CD 271	0.095 - 0.105%	Start Middle End	0.101% 0.101% 0.101%
Methyl parahydroxybenzoate	0.09 - 0.11%	Start Middle End	0.097% 0.097% 0.097%

CONCLUSION

The product was accepted.

HEAD
ANALYTICAL SERVICE

RESPONSIBLE
PHARMACIST

CHIMIE ANALYTIQUE

RAPPORT D'ANALYSE

DESTINATAIRE : C. RAYBAUT		DATE : 24/6/92
N° : 2391	RÉFERENCE ÉCHANTILLONS: Gel CD 271; 0.1% "A" N° 555089/F1 Gel CD 271; 0.1% "B" N° 524635/2/F8 Study CR 92140 (End of study)	PAGE 1 de 1

RÉSULTATS :

HPLC ASSAY FOR CD 271

Method CIRD-M-007/271F-2V

Tube "A"	0.100% 0.098%
Tube "B"	0.103% 0.101%

COMMENTAIRES :	PIECE(S) JOINTES :

ANALYSTE :	RÉFERENCE CAHIER :	APPROBATION :
M. VION		

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

APPENDIX IV

QUALITY ASSURANCE CERTIFICATE

QUALITY ASSURANCE AUDIT CERTIFICATE

PROJECT : CD 271 GEL

STUDY N°: CR 92140
CPCAD

TITLE : 21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

This report was thoroughly audited against the requirements of the approved protocol, internal and regulatory (French) Good Clinical Practice guidelines and against supportive raw data.

DATE OF AUDIT	AUDITED BY	REPORT SENT TO MANAGEMENT
27/07/92 (raw data / final report)	F. WATTS	06/08/92

Based on this audit, I hereby certify that this report describes the materials and methodology used and reflects the results obtained correctly and completely.

6/8/92

N. KAIL
Quality Assurance Manager

STUDY REPORT CR 92140

21-DAY REPEATED APPLICATION SKIN IRRITATION TESTING OF TWO 0.1% CD 271 GELS

APPENDIX V

APPROVAL BY THE ETHICS COMMITTEE

COMITE CONSULTATIF DE PROTECTION DES PERSONNES
DANS LA RECHERCHE BIOMEDICALE
C.H.R. - Hôpital Pasteur
B.P. 069 - 06002 NICE CEDEX 01
T. 92.03.81.46

NICE, le 6 mai 1992

Projet de Recherche
Enregistré sous le numéro : 92.26

Le Comité a été saisi le 17 avril 1992 par le Docteur RAYBAUD d'une demande d'avis pour un projet de recherche intitulé :

Test d'évaluation de la tolérance cutanée après application itérative de 21 jours en peau saine de deux formulations Gel du CD 271 à 0,1 %

dont le Promoteur est : CIRD GALDERMA
Numéro de Protocole : CR92140

Le Comite a examiné les informations relatives à ce projet lors de sa séance du 5 mai 1992.

Ont participé à la délibération :

Monsieur AUCLAIR, Pharmacien, Industrie Pharmaceutique
Madame BAJARD, Pharmacien, Centre A. Lacassagne
Madame CAIRASCHI, Psychologue, Centre A. Lacassagne
Dr DOR, Praticien, Centre Hospitalier d'Antibes
Monsieur LE MADEC, Infirmier, C.H.S. Sainte-Marie
Monsieur l'Abbé POYARD
Monsieur PUCHOIS, Industrie Pharmaceutique
Dr QUARANTA, Praticien, C.H.U., Nice

Le Comité a adopté la délibération suivante :

AVIS FAVORABLE

Néanmoins, avant le début de l'étude, veuillez mettre en conformité la formulation gel testée numérotée 526.635/2 à la page 2 et numérotée 524.635/2 à la page 4.

Par ailleurs, conformément à la Loi Huriet, veuillez rajouter dans le consentement éclairé, la référence au fichier des volontaires sains.

Le Président de Séance,

J.F. QUARANTA,

COMITE CONSULTATIF
DE PROTECTION DES PERSONNES
DANS LA RECHERCHE BIOMEDICALE
HOPITAL PASTEUR NICE