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
Effect of CD08100/02 3 % gel versus placebo in subjects presenting with erythematotelangiectatic rosacea over a 4-week treatment period</td></tr>
<tr><td>Project Name</td><td>Project Number</td><td>Clinical Phase</td></tr>
<tr><td>CD08100/02</td><td>265</td><td>Phase II therapeutic exploratory (IIa)</td></tr>
<tr><td colspan="2">Investigational Product
(name, formulation, concentration)</td><td>Comparator Product
(name, formulation, concentration)</td></tr>
<tr><td colspan="2">Solaraze® (CD08100/02, Diclofenac sodium 3 % gel)</td><td>Placebo (CD0036 NF gel)</td></tr>
<tr><td>Subject Population/Indication</td><td>Treatment/Study Duration</td><td>Dose</td></tr>
<tr><td>Male and female subjects with moderate to severe erythematotelangiectatic rosacea (ETR)</td><td>Approximately 4 months from FSI to LSO.
Study duration for each subject of 10 weeks maximum including a up to 4-week screening period, a 1-week run-in phase, a 1-week wash-out phase and a 4-week treatment phase</td><td>Daily dose: 2 mg/cm² on each half face of 200 cm²</td></tr>
<tr><td colspan="3">Design</td></tr>
<tr><td colspan="3">Single-centre, randomized, investigator-blinded, placebo-controlled study using intra-individual comparison (right side of face versus left side)</td></tr>
<tr><td colspan="2">Study Initiation Date
(first subject enrolled)</td><td>Study Completion/Termination Date
(last subject completed)</td></tr>
<tr><td colspan="2">24th October 2011</td><td>23rd December 2011</td></tr>
<tr><td colspan="3">EUDRACT N°: 2011-002057-65
IND No.: RD.03.SPR.40161E</td></tr>
</table>

This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents. This abbreviated Clinical Study Report (aCSR) complies with the International Conference on Harmonisation (ICH) E-3 and

the FDA "Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications".

Appropriate investigator signature(s) are in appendix 16.1.5.

Authors:

Authors	**Signature**	**Date**
Dr. Dorothea Wilhelm (proDERM GmbH)		July 9th, 2012
Agnes Himmelmann (proDERM GmbH)		July 9th, 2012

Approvals	**Signature**	**Date**
Medical Expert, Dr Christophe Piketty (Galderma R&D Sophia Antipolis Site)		17/7/2012
Clinical Scientist, Alexandra Lamquin (Galderma R&D Sophia Antipolis Site)	PO	July, the 17th 2012
Statistician Philippe Briantais (Galderma R&D Sophia Antipolis Site)		July, the 17th 2012

Distribution:

Original Report:	Archives (Galderma R&D Sophia Antipolis Site)
Core Report:	Clinical Scientist, Alexandra Lamquin (Galderma R&D Sophia Antipolis Site)
Summary:	Ethics Committee and Competent Authorities, Principal Investigator, Dr Kirstin Deuble-Bente (proDERM)

2 SYNOPSIS

NAME OF COMPANY	***For regulatory use only***
GALDERMA R&D	
NAME OF FINISHED MEDICINAL PRODUCT	
Solaraze®	
NAME OF ACTIVE INGREDIENT(S)	
Diclofenac Sodium	
Title of study:	Effect of CD08100/02 3 % gel versus placebo in subjects presenting with erythematotelangiectatic rosacea over a 4-week treatment period

- **Investigators**

Dr. Kirstin Deuble-Bente, Principal investigator

Dr. U. Theissen, Prof. Dr. K.-P. Wilhelm, Sub-investigators

- **Study Centre**

proDERM GmbH

- **Clinical Phase**

Phase IIa

- **Study Period**

  - **Date of first subject screened:** 24th October, 2011
  - **Date of last subject completed:** 23rd December, 2011

- **Study Objective(s)**
- **Efficacy objective:**

  - To assess the efficacy of CD08100/02 3% gel versus placebo gel after a 4-week treatment period, in subjects presenting with moderate to severe ETR.

- **Safety objective:**

  - To evaluate the safety of CD08100/02 3% gel by adverse events (AE) reporting, physical examination and vital signs.

- **Study Design**

This study was a single-centre, randomized, investigator-blinded, placebo-controlled study using intra-individual comparison (right side of face versus left side).

Total study duration for one subject was approximately 10 weeks, including a screening period of up to 4 weeks, a 1-week run-in phase, a 1-week wash-out phase and a 4-week treatment period.

- **Number of Subjects (planned and analyzed)**

In the protocol, it was planned to enrol 25 subjects in the run-in period of the study to ensure that at least 13 subjects complete the treatment period.

In fact, 33 subjects were screened, 23 randomized and 20 completed the study.

Table 1: Disposition of Subjects

Completion Status	Total
Screened (ICF signed)	33
Randomized*	23 (100.0)
Normal Study Completion	20 (87.0)
Premature Discontinuation	3 (13.0)
Adverse Event or SAE	0 (0.0)
Non-medical reason (inclusion criteria no longer met after run-in phase)	3 (13.0)
Subject withdraw consent	0 (0.0)
Non-compliance	0 (0.0)
Others	0 (0.0)
Assessable for efficacy (ITT)	20 (87.0)
Assessable for efficacy (PP)	20 (87.0)
Assessable for safety	20 (87.0)

ICF = informed consent form, SAE = serious adverse event, ITT= Intent to Treat, PP = per-protocol population; data source: Table 14.1.1

* At Day -14 (start of placebo run-in phase), each subject who fulfilled all inclusion/non-inclusion criteria were assigned a Randomization Number. The ITT population was defined as all subjects who were randomized and eligible in the treatment period. However, among the 23 subjects randomized at D-14, three of them (Randomization Nos. 3, 13 and 23) were excluded from any populations (ITT, PP and Safety) because they did not fulfil the inclusion criteria “Erythema Severity Score ≥ 3” after the run-in phase anymore. During the treatment period, no major deviations

were observed, consequently all subjects of ITT population (N=20) were also considered as PP population.

- **Diagnosis and Key Inclusion Criteria**

To be eligible for the study, subjects had to fulfil the following criteria at screening and/or day –14 visit (start of placebo run-in phase):

1. The subject had to be male or female adult of at least 18 years old
2. The subject had to present a moderate to severe ETR characterized by:
   - A persistent erythema on the face
   - An erythema severity score graded of at least 3 on a 5-point scale (from 0 to 4) on each cheek
   - The same erythema severity score on each cheek
   - A possible presence of telangiectasia, flushing/blushing, edema
   - No significant history of inflammatory lesions (papules and/or pustules) in the 3 months before the screening visit
   - Less than three inflammatory lesions on the face at the day-14 visit (start of placebo run-in phase)

At the baseline visit (day 1), the subjects also had to fulfil the inclusion criteria n° 2 to receive the study products during the treatment phase.

- **Test Product Dosage Form**

Table 2: Test Product Dosage Form

	Investigational Product	**Placebo**
Trade Name	Solaraze®	NA
Name of Drug Substance (INN)	Diclofenac sodium	NA
Internal code	CD08100/02	CD0036 NF gel
Pharmaceutical Form	Gel	Gel
Concentration	3 %	NA
Packaging (type and size)	25 g tubes	30 g tubes
Storage Conditions	Store below 25°C	Store below 25°C do not freeze or refrigerate
Dosage (total daily dose)	400 mg (2mg/cm² on 200 cm²)	400 mg (2mg/cm² on 200 cm²)
Dose regimen		
Route	Topical	Topical
Frequency	Once daily application	Once daily application
Duration of administration	4 weeks (19 applications)	1 week run-in period + 4 weeks of treatment period (24 applications)
Location of treated area	Hemi-face	Hemi-face
Formula No.	NA	0569.0005P

- **Efficacy Criteria**

  - **Primary Efficacy Variable**
    - Change from baseline in cheek erythema severity score for each cheek on day 26

  - **Secondary Efficacy Variables**
    - Cheek erythema severity score and the change from baseline for each side of the face at each evaluation visit
    - Change from baseline in the cheek erythema surface area for each side of the face at each evaluation visit
    - Change from baseline in the telangiectasia score using Dermascore for each side of the face at each evaluation visit
    - Edema score for each side of the face at each evaluation visit
    - Inflammatory lesion count (papules/pustules) for each side of the face at each evaluation visit
    - Changes from baseline in mean a* colorimetric parameter for each cheek at each evaluation visit
    - If necessary, the change from baseline in the mean b* and L* colorimetric parameters for each cheek at each evaluation visit
    - Subject's and investigator's preference regarding the whole pathology at day 26 (final visit/early discontinuation)
    - Number of flushing/blushing episodes per week, severity and duration for each side of the face at each evaluation visit
    - Functional signs assessment for each side of the face at each evaluation visit

  - **Exploratory Efficacy Variables**
    - Cheek erythema severity score from photographic scale for each side of the face at each evaluation visit
    - Kinetics of erythema evolution for each side of the face at day 3/4
    - Telangiectasia severity score from photographic scale for each side of the face at each evaluation visit
    - Subject's and investigator's erythema preference for each side of the face on day –9 and day 26 (final visit or early discontinuation)
    - Flushing from flush model at day 1/2 (baseline) and day 24/25 or earlier in case of discontinuation

- Photographs taken with VISIA CR at each evaluation visit

▪ Safety Criteria

- Occurrence of AEs
- Physical examination
- Vital signs

▪ Principal Statistical Methods

The erythema score of the right and left cheek was analyzed. The change from baseline in the erythema score at day 26 (ITT, LOCF, PP-observed cases) was analyzed by t-test for paired data. All tests were two-sided and the 0.05 probability level was used to declare significance.

Treatment-Emergent Adverse Events (TEAE) defined as those with onset occurring the day of first use or later (in the treatment period) had to be tabulated in frequency table by System Organ Class (SOC) and Preferred Term (PT) based on the MedDRA dictionary. Additional summary tables had to be provided for TEAEs that were considered as severe, serious (SAEs), and those leading to subject discontinuation. AEs and related AEs were summarized for each SOC.

The treatment period was analyzed separately from the run-in period.

▪ Sample Size

- **Historical Data**

One previous study (Galderma R&D, RD.03.SPR.40042) with a similar design, using a 5-point scale (none to severe) to assess erythema on left and right cheeks, was performed comparing Ondansetron to its vehicle. The between-subject standard deviation of the right/left differences in term of change from baseline for the erythema score was estimated at 0.5 after 4 weeks of treatment.

- **Assumption**

It was estimated that a drug with an effect on erythema versus placebo of 15 % may be of interest. Assuming a mean baseline erythema score of 3.25, this corresponds to an approximate difference of 0.5 points. Assuming a standard deviation of the between treatment paired differences of 0.5, this led to an effect size of 1.

- **Sample Size Calculation**

Using the standard formula for paired t-test from nQuery Advisor® 4.0 to compare mean difference, and also using an estimated effect size of 1 (difference/SD), a power set at 90 % and a type I error at 5 % two-sided, 13 subjects were necessary.

▪ Summary of Results

- **Demographic and Baseline Data**

Table 3: Demographics (SP; n = 20)

		Total (n = 20)
Age(years)	**N**	20
	Mean ± SD	50.3 ± 14.4
	range	27 to 75
Gender	**N**	20
	Female	18 (90.0)
	Male	2 (10.0)

SP = safety population, SD = standard deviation

Table 4: Baseline disease characteristics (PP; n = 20)

Baseline (Day 1) Characteristics of the Disease		**Placebo (n = 20)**	**Solaraze® (n = 20)**
Erythema Severity Score on Cheek	**N**	20	20
	Mean ± SD	3.3 ± 0.4	3.3 ± 0.4
	range	3 to 4	3 to 4
Cheek Erythema Surface Area [%]	**N**	20	20
	Mean ± SD	64.3 ± 24.1	65.1 ± 24.0
	range	30.0 to 95.0	30.0 to 97.0
Telangiectasia Score using Dermascore	**N**	20	20
	Mean ± SD	4.4 ± 1.0	4.4 ± 1.0
	range	3 to 6	2 to 6
Counts of Papules	**N**	20	20
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0
	range	0 to 0	0 to 0
Counts of Pustules	**N**	20	20
	Mean ± SD	0.0 ± 0.0	0.0 ± 0.0
	range	0 to 0	0 to 0
Counts of Flushing/Blushing Episodes per Week	**N**	20	20
	Mean ± SD	9.8 ± 6.8	9.8 ± 6.8
	range	1 to 28	1 to 28

PP = per-protocol population, SD = standard deviation

- **Efficacy Results**

Primary analysis of efficacy is based on changes of erythema severity scores from baseline (day 1) after 4 weeks of treatment (day 26).

The results relative to erythema severity score are summarized in the following table (Table 5). No efficacy of the test product was shown in this study.

Table 5: Results of paired t-Test for Comparisons of Treatments regarding Changes of Erythema Severity Score (PP; n = 20)

Assessment	Mean Erythema Severity Score		Mean Changes from Day 1		Differences between Changes from Day 1 (Prd – Pbo)				p-value of two-sided paired t- Test
	Prd	Pbo	Prd	Pbo	Mean	SD	Min	Max	
Day 1	3.3	3.3	--	--	--	--	--	--	--
Day 5	3.3	3.3	0.0	0.0	0.0	0.0	0.0	0.0	n.e.
Day 12	3.4	3.4	0.2	0.2	0.0	0.0	0.0	0.0	n.e.
Day 19	3.3	3.3	0.0	0.0	0.0	0.0	0.0	0.0	n.e.
Day 26	**3.3**	**3.3**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**0.0**	**n.e.**

Prd = Solaraze®, Pbo = placebo, PP = per-protocol population; bold = primary objective, n.e. = not evaluable, SD = standard deviation

Regarding all the other investigated parameters (cheek erythema surface area, telangiectasia and edema severity scores, inflammatory lesions count, colorimetric parameters a*, b* and L*, flushing episodes, functional signs such as itching, dryness sensation, stinging as well as investigator's and subject's preferences regarding the erythema and the whole pathology), no statistically significant differences between Solaraze® and placebo were shown.

- **Safety Results**

Table 6: Summary of Treatment Emergent Adverse Events (SP; n = 20)

	Placebo (n = 20)		Solaraze® (n = 20)		Total (n = 20)	
	events	subjects	events	subjects	events	subjects
	n	n (%)	n	n (%)	n	n (%)
All AEs	8	7 (35.0)	9	8 (40.0)	9	8 (40.0)
Related AEs	0	0 (0.0)	1	1 (5.0)	1	1 (5.0)
All dermatological AEs	1	1 (5.0)	2	2 (10.0)	2	2 (10.0)
Related dermatological AEs	0	0 (0.0)	1	1 (5.0)	1	1 (5.0)
All serious AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Related serious AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Severe AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Related severe AEs	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
AEs of Special Interest	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Related AEs of Special Interest	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
AEs leading to discontinuation	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Related AEs leading to discontinuation	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Deaths	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

SP = safety population, AE = adverse event

Nine (9) non-serious TEAEs (Treatment-Emergent Adverse Events) were documented in this study in total.
One treatment related dermatological AE was documented for a Solaraze® treated area (SIN 027/Randomization No. 21). It was described as paraesthesia (tickling and burning) with no visible changes on the cheek. The severity was characterized as moderate and the pattern as intermittent. It lasted for 19 days. No action was taken and the patient recovered without sequelae.

No clinically relevant changes regarding blood pressure and pulse rate were seen between screening and study termination. Moreover, no pathological findings regarding skin (other than ETR), lungs, abdomen, eyes, ears, nose, throat, neurological function, musculoskeletal system, lymph nodes and cardiovascular system were seen neither at screening nor at study termination.

- **Conclusion**

No efficacy of Solaraze® in erythematotelangiectatic rosacea was shown during the study, in comparison with placebo after 4 weeks of daily applications.

Placebo and test product were not irritant in this study.

No safety issue was identified regarding physical examination, control of vital signs and reporting of Adverse Events.

During the study, nine (9) adverse events were reported of which one was related to Solaraze® treatment. There were no deaths, no SAE and no subject discontinuation from the study due to an Adverse Event.