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EVALUATION OF THE ANTI-WRINKLE AND FIRMING EFFECTS OF A COSMETIC PRODUCT (NIGHT CREAM)

Report (version 1):	**#09E0901, December 7, 2009**
Price proposal:	**#09D0901-3**
Product:	**Rivoli Night cream Lab-00008.8, Batch #67503**
Form:	**Beige fluid emulsion**
Application zone:	**Face**
Sponsor:	**TORSTONE SA c/o INDUCHEM AG Industriestrasse 8A, CH-8604 Volketswil SWITZERLAND**
Study monitor:	**Mr Giorgio DELL'ACQUA DELL'ACQUA CONSULTING**
Investigation site:	**Laboratoire DERMSCAN Domaine Scientifique de la Doua 56 Boulevard Niels Bohr 69623 Villeurbanne Cedex FRANCE**
Study Managers:	**Mrs Anne VIOLA / Carine KURDIAN avi@dermscan.com / cku@dermscan.com**

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Document: 1/2
(document including 42 pages)

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Quality control

CERTIFICAT DE CONTROLE QUALITE

QUALITY CONTROL AUDIT STATEMENT

Numéro de l'étude clinique / *Clinical study number :*	09E0901
Date de début de l'étude / *Study start date :*	September 25, 2009
Date de fin de l'étude / *Study completion date :*	November 19, 2009

L'étude référencée ci-dessus a été conduite conformément aux règles des Bonnes Pratiques Cliniques (BPC-ICH) et aux procédures opératoires standardisées de DERMSCAN.

The study listed above was conducted in conformance with Good Clinical Practice (GCP-ICH) and DERMSCAN standard operating procedures.

La personne habilitée à exercer le contrôle qualité final atteste du respect des règles et des procédures nommées ci-dessus.

The Quality control Auditor testifies to the respect of the rules, the standards and procedures listed above.

Nom / *Last name* :	NATALIZIO
Prénom / *First name* :	Audrey
Date / *Date* :	December 17, 2009
Signature / *Signature* :	Natalizio

Summaries

RESUME DU RAPPORT D'ETUDE N°09E0901

	Promoteur : TORSTONE SA **Adresse :** c/o INDUCHEM AG Industriestrasse 8A, CH-8604 Volketswil SUISSE	**Investigateur : DERMSCAN** **Adresse :** Domaine Scientifique de la Doua Bâtiment CEI 2 56, boulevard Niels Bohr 69623 Villeurbanne Cedex - FRANCE
Titre de l'étude	**EVALUATION DES EFFETS ANTI-RIDES ET RAFFERMISSANT D'UN PRODUIT COSMETIQUE (CREME DE NUIT)**	
Produit	**Référence :** Rivoli Night cream Lab-00008.8, Lot 67503.	**Forme galénique :** Emulsion fluide beige.
Dates de l'étude	Du 25 septembre au 19 novembre 2009.	
Objectifs	- Evaluer l'effet anti-rides du produit étudié. - Evaluer son effet raffermissant. - Evaluer subjectivement ses caractéristiques organoleptiques, son efficacité, sa tolérance et son utilisation ultérieure. - Illustrer son effet visuel attendu.	
Plan expérimental	Etude en ouvert et en intra-individuel.	
Critères d'évaluation	- Analyse des paramètres du relief cutané à l'aide du Skin Image Analyser® et du logiciel Quantirides®. - Illustration de l'effet visuel attendu par macrophotographies.	**Cinétique** : J0-J14-J28-J56. **Méthodologie** : Avant / Après. **Zones de mesure** : Front. **Fréquence d'application** : Une fois par jour (le soir).
	- Analyse des propriétés biomécaniques de la peau à l'aide du Cutomètre®.	**Cinétique** : J0-J28-J56. **Méthodologie** : Avant / Après. **Zones de mesure** : Tempes. **Fréquence d'application** : Une fois par jour (le soir).
	- Evaluation subjective avec un questionnaire.	**Cinétique** : J56. **Méthodologie** : Avant / Après. **Zones de mesure** : Visage. **Fréquence d'application** : Une fois par jour (le soir).
Population étudiée	Nombre de volontaires analysés : -21 à J0 et J28 et 20 à J56 pour l'effet raffermissant et les macrophotographies; -21 à J0 et J14 et 20 à J28 et J56 pour l'effet anti-ride ; -20 pour le questionnaire d'évaluation subjective.	
	Age moyen : 56±1 ans (entre 42 et 64 ans).	
	Critères principaux d'inclusion : • Sexe : féminin. • Age : compris entre 35 et 65 ans. • Sujet ayant des rides au niveau du front.	

Résultats - Conclusion	**Dans les conditions de l'étude, le produit "Rivoli Night cream Lab-00008.8, Lot 67503":** ➢ **a induit un <u>effet anti-rides significatif dès 14 jours d'utilisation</u>; caractérisé par:** ▪ **une diminution significative du nombre de rides profondes de -37% en moyenne, diminution observée chez 67% des volontaires;** ▪ **une diminution, limite significative, de la profondeur des rides profondes de -6% en moyenne, diminution observée chez 70% des volontaires;** ▪ **une diminution significative de la surface ridée totale de -40% en moyenne, diminution observée chez 81% des volontaires.** **Cet effet est <u>de nouveau mesuré après 56 jours d'utilisation avec</u> :** ▪ **une diminution significative du nombre de rides moyennes de -28% en moyenne, diminution observée chez 65% des volontaires;** ▪ **une diminution significative du nombre de rides profondes de -38% en moyenne, diminution observée chez 75% des volontaires;** ➢ **n'a pas modifié en moyenne les propriétés biomécaniques de la peau;** ➢ **a satisfait une majorité des volontaires pour:** ▪ **<u>ses caractéristiques organoleptiques</u> : aspect (90%) et texture (85%) agréables, étalement (95%) et pénétration (90%) faciles;** ▪ **<u>son efficacité immédiate</u> : effet tenseur/liftant (90%) et sensation de fraîcheur (85%);** ▪ **<u>son efficacité après 56 jours d'application</u> : 90% des volontaires ont constaté une amélioration globale de l'état et de l'aspect de la peau et 70% ont trouvé leur peau apaisée, décongestionnée, 65% des volontaires ont trouvé les signes de fatigue atténués et 80% ont trouvé leur peau plus hydratée.** **55% des volontaires continueraient à utiliser le produit et 60% l'achèteraient.**

Carine KURDIAN **Assistante Responsable d'Essais**	**Date** 7/12/09	**Signature**

SUMMARY OF THE STUDY REPORT #09E0901

	Sponsor: TORSTONE SA **Address:** c/o INDUCHEM AG Industriestrasse 8A, CH-8604 Volketswil SWITZERLAND	**Investigator: DERMSCAN** **Address:** Domaine Scientifique de la Doua Bâtiment CEI 2 56, boulevard Niels Bohr 69623 Villeurbanne Cedex - FRANCE

Study Title	**EVALUATION OF THE ANTI-WRINKLE AND FIRMING EFFECTS OF A COSMETIC PRODUCT (NIGHT CREAM)**		
Product	**Reference:** Rivoli Night cream Lab-00008.8, Batch #67503.	**Galenic form:** Beige fluid emulsion.	
Study dates	From September 25 to November 19, 2004.		
Objectives	- To evaluate the anti-wrinkle effect of the studied product. - To evaluate its firming effect. - To subjectively evaluate its organoleptic properties, its efficacy, its tolerance and its future use. - To illustrate its visual expected effect.		
Experimental plan	Open and intra-individual study.		
Assessment criteria	-Analysis of the cutaneous relief parameters using Skin Image Analyser® and Quantirides® software. -Illustration of the visual expected effect by macrophotographs.	**Kinetics**	D0-D14-D28-D56.
		Methodology	Before / After.
		Measurement zone	Forehead.
		Application frequency	Once- daily (on the evening).
	-Analysis of the skin biomechanical properties using Cutometer®.	**Kinetics**	D0-D28-D56.
		Methodology	Before / After.
		Measurement zone	Temples.
		Application frequency	Once- daily (on the evening).
	-Subjective evaluation using questionnaire.	**Kinetics**	D56.
		Methodology	Before / After.
		Measurement zone	Face
		Application frequency	Once- daily (on the evening).
Studied population	Number of subjects analyzed: -21 on D0 and D28 and 20 on D56 for firming effect and macrophotographs, -21 on D0 and D14 and 20 on D28 and D56 for anti-wrinkle effect ; -20 for subjective evaluation questionnaire.		
	Average age: 56±1 years (between 42 and 64 years old).		
	Main inclusion criteria: • Sex: female. • Age: between 35 and 65 years old. • Subject having wrinkles on the forehead.		

Results - Conclusion	**Under these study conditions, product "Rivoli Night cream Lab-00008.8, Batch #67503":** ➢ **induced a <u>significant anti-wrinkle effect from 14 days of use</u>, characterized by;** ▪ **a significant decrease in the number of deep wrinkles of -37% on average, decrease observed in 67% of subjects;** ▪ **a decrease, limit in significance in the depth of deep wrinkles of -6% on average, decrease observed in 70% of subjects;** ▪ **a significant decrease in the total wrinkled surface of -40% on average, decrease observed in 81% of subjects;** **<u>This effect was again measured after 56 days of use</u>, with:** ▪ **a significant decrease in the number of medium wrinkles of -28% on average, decrease observed in 65% of subjects;** ▪ **a significant decrease in the number of deep wrinkles of -38% on average, decrease observed in 75% of subjects;** ➢ **did not modify on average skin biomechanical properties;** ➢ **satisfied a majority of the subjects for:** ▪ **its <u>organoleptic characteristics</u>: pleasant aspect (90%) and texture (85%), easy spreading (95%) and penetration (90%);** ▪ **<u>its immediate efficacy</u>: tensor/lifting effect (90%) and freshness sensation (85%);** ▪ **<u>its efficacy 56 days after application</u>: 90% of the subjects noticed a global improvement in the skin state and aspect, 70% found their skin appeased, relieved congestion, 65% found their signs of tiredness attenuated and 80% found their skin more moisturized.** **55% of the subjects would continue to use this product and 60% of the subjects would buy it.**

Carine KURDIAN **Trial Manager Assistant**	**Date** 12/07/09	**Signature**

Aim(s) of the study

Method(s)

1. AIMS

1.1. Primary objectives

The primary objectives of this study were to evaluate the anti-wrinkle and firming effects, after 14, 28 and 56 days of use of product "Rivoli Night cream Lab-00008.8, Batch #67503".

1.2. Secondary objectives

The secondary objectives of this study were, for the studied product:

- to evaluate the subjective appreciation of its organoleptic characteristics, its efficacy, its tolerance and its future use,
- to illustrate its visual expected effect.

2. METHODS

2.1. Trial period

Product reception:	August 28, 2009.
Beginning of the study:	September 25, 2009.
End of the study:	November 19, 2009.
First results by e-mail:	November 27, 2009.

2.2. Experimental plan

This was an open, intra-individual study; each subject was her own control.

2.3. Assessment criteria

2.3.1. Primary criteria

- Study of the different cutaneous relief parameters variations (number and depth of micro-relief furrows, medium wrinkles and deep wrinkles and total wrinkled surface) using Skin Image Analyser® (S.I.A®) with the QuantiRides® software (Monaderm, Monaco).
- Study of skin biomechanical properties variations (suppleness, tension, tonicity, firmness) using Cutometer® (COURAGE & KHAZAKA).

2.3.2. Secondary criteria

- Analysis of the subjects' answers to a subjective evaluation questionnaire.
- Evaluation of the anti-wrinkle effect by macrophotographs.

2.3.3. Principles

2.3.3.1. Anti-wrinkle effect

Polymer silicone skin's prints (Silflo®) were taken on the studied zone, before product use and at each time of measurement, then studied using Skin Image Analyser® (S.I.A®).

An oblique lighting of 35° brings shadows on the replica surface. These shadows are observed with a digital camera linked to a computer. A 1 cm^2 area is studied.

The digitized picture obtained is analysed in grey levels and allows to obtain different parameters of the skin surface relief: the parameters studied with the QuantiRides® software (Monaderm, Monaco) are the **total wrinkled surface** (in mm^2), the **number** and the **average depth** (in µm) **of cutaneous microrelief furrows, medium wrinkles and deep wrinkles**.

Microrelief furrows have a depth lower than 55 μm. Median wrinkles have a depth ranging between 55 and 110 μm and deep wrinkles have a depth lower than 110 μm. The minimal surface of a furrow so that it is taken into account is arbitrarily fixed to 0.03 mm^2.

A **decrease** in the parameters of micro-relief furrows characterises a **smoothing effect**.
A **decrease** in the parameters of medium or deep wrinkles and of the total wrinkled surface characterises an **anti-wrinkle effect**.

2.3.3.2. Skin biomechanical properties

Skin has two rheological characteristics:

- a visco-elastic property with high elasticity,
- a natural tension which varies depending on the zone.

The network formed by tension lines in the skin is called the Langer network.

The rheological properties of conjunctive tissue stem from its structure: basically, a three dimensional network of collagen and elastin fibers.

The only method capable of measuring variations, on man, induced by active pharmaceutical or topic agents over time is a non-invasive, *in vivo*, rheological evaluation.

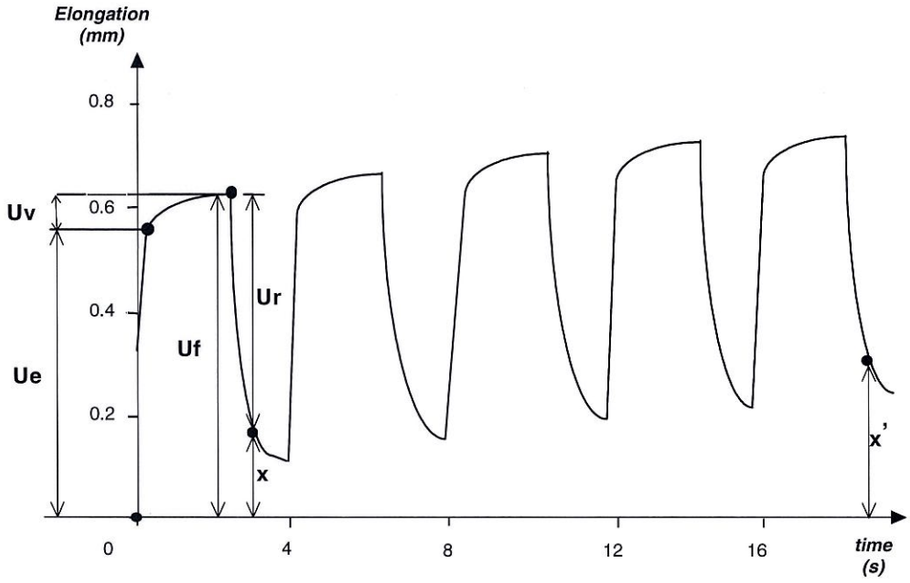
The procedure used enables evaluation of variations in the biological extensibility and elasticity of superficial cutaneous layers.
Measurement is done with a SEM 575 CUTOMETER® (COURAGE & KHAZAKA) connected to a computer.
The technique consists in skin aspiration by a measurement probe. These measurements define different parameters characterizing the biomechanical properties of tegument.

The skin is sucked into the orifice of a probe by constant vacuum pressure for a set length of time. The depth to which the skin penetrates into the probe is measured by two optical prisms located at the opening of the probe's orifice to eliminate the effects of friction and mechanical strain.
The constant vacuum pressure of the probe is

- 200 mbar for measurements on the temples, forearms or chest.
- 500 mbar for measurements on thighs and belly.

The curve displayed on the screen should have the profile presented below.

Cycle of five deformations of the skin measured with the Cutometer®.



Rheological parameters obtained after five skin aspirations are:

- immediate elongation: Ue (mm)
- delayed elongation: Uv (mm) avec Uv = Uf - Ue,
- **total elongation:** **Uf (mm) avec Uf = Ue + Uv,**
- immediate retraction: Ur (mm) avec Ur = Uf - X,
- residual elongation after 1st cycle: X (mm)
- residual elongation after 5th cycle: X' (mm).

The following biomechanical parameters could be analyzed:

- **tension** (-ΔUf): if the total elongation decreases, skin is tighter.
- **firmness** (ΔUr/Uf) : if the immediate retraction/total elongation ratio increase, skin is firmer.
- **tone** (-ΔX) : if the residual elongation decreases, skin is more tonic.
- **suppleness** (ΔUe) : if the immediate elongation increases, skin is more supple.

Each measurement is an average of three acquisitions.

2.3.3.3. Subjective evaluation questionnaire

A subjective evaluation questionnaire, prepared by the clinical trial center and submitted to the sponsor, was completed by the subjects at the end of the study (D56) to subjectively evaluate the organoleptic characteristics of the studied product, its global efficacy, its tolerance and its future use.

2.3.3.4. Macrophotography

The digital camera used was a camera of the type Nikon D70.

The photographs were taken in a standardized, indirect light. Aperture, speed and distance of the camera were also standardized.

The control of the repositioning takes place directly on data-processing screen thanks to a simultaneous visualization of the images at various times of acquisition.

2.4. Methods pertinence

2.4.1. Anti-wrinkle effect

Different methods exist to quantify cutaneous relief. Among them, the Skin Image Analyser® (SIA) is a classic method based on the study of shadows from the replica brought by 35° lighting.
Silicone prints in Silflo® are the perfect replica in negative of the cutaneous relief. The consistency of this gel before polymerization allows to insinuate in all the cutaneous asperities, then to definitively solidify itself and in state.
This is a simple method, non invasive, the prints being able to be preserved without deterioration before the analyze with QuantiRides® software. Principal parameters characterizing the cutaneous relief are quantified by the software, which allows the study of variations related to cosmetic product use.

2.4.2. Skin biomechanical properties

The study of skin biomechanical properties allows to determine the effects of some smoothing or tensor "actives." It has been evidence this way the very pronounced effect of the massage, which redirects collagen fibers and that of anhydrous, emulsified or totally aqueous vehicles whose impact on biomechanical properties, as well as on hydration, is significant. Techniques by torsion (Dermal Torque Meter®) or aspiration (Cutometer®) provide atraumatic, rapid and reproducible measurements. If an experienced technician exerts perfect pressure on the sensor, the interpretation of the obtained curves allows to reliably evaluate the efficacy of a minimum of two- or three-weeks treatment.

2.4.3. Subjective evaluation questionnaire

Answers given by the subjects to a subjective evaluation questionnaire are used to evaluate the characteristics, the efficacy and the tolerance of the studied product. These subjective criteria give, in particular, accurate information regarding product appreciation.

2.4.4. Macrophotographs

The digital camera takes precise and reproducible macrophotographs. It is used to provide images taken directly with a control in real time, which allows the photograph to be adjusted.

2.5. Subject selection

2.5.1. Number of subjects

The study was done on 20 subjects minimum, at the sponsor's request.

2.5.2. Inclusion criteria

General criteria
Healthy subject.
Subject having given her informed, written consent.
Cooperative subject, aware of the necessity and duration of controls so that perfect adhesion to the protocol established by the clinical trial center could have been expected.
Specific criteria
Sex: female
Age: between 35 and 65 years old.
Subject having horizontal lines on the forehead.

2.5.3. Non-inclusion criteria

Pregnant or nursing woman or woman planning to get pregnant during the study.
Cutaneous pathology on the studied zone (eczema, etc).
Subject using, on the measured zone, any product acting on the cutaneous relief (anti-wrinkle cream) or having stopped one for less than 1 month.
Subject having done facial injections and/or palpebral lifting.
Subject having changed, started or stopped her oral contraception or any hormonal treatment for less than 1.5 month.
Known allergy to cosmetic or dermopharmaceutical products.
Any treatment that could interfere with the evaluation of the efficacy or the tolerance of the studied product.
Subject having had a surgical intervention with general anaesthesia in the month which precedes the beginning of the study.

2.5.4. Compliance assessment

If the protocol was not respected and if the deviation was minor, the technician or the investigator in charge of the study warned the subject of the importance of respecting the prescribed protocol. If the subject persisted or if the deviation was major, the subject was declared non-compliant. In this case, the subject was removed from the study for non-compliance.

Under normal conditions of use (application of the product at home), no compliance control could be carried out during the study. However, the subject filled in every day the daily log and noticed the number of use.

2.5.5. Associated treatment during the study

No use of dermopharmaceutical or cosmetic products other than the studied product was authorized on the face during the study, except the usual cleansing product.
No excessive exposure to sunlight or UV-rays during the study was authorized.

2.6. Operational aspect

2.6.1. Trial schedule

On D0

- Subjects came to the laboratory without having applied any product to the face since the previous evening.
- They read, signed and dated the information sheet (instructions on the product use and restrictions related to the study) and informed consent forms in duplicate. These documents were also signed and dated by the person who conducted the informed consent discussion. The subjects received a copy.
- Verification of inclusion and non-inclusion criteria by the technician in charge of the study..
- Definition of one studied zone on the forehead and another one on a temple.
- Implementation of a zoomed photograph of the studied zone of forehead.
- Implementation of print with Sifflo® gel on the horizontal lines of forehead.
- Measurements of skin biomechanical properties using Cutometer® on the defined temple.
- Distribution of the daily log (D0-D13) and the studied product to the subjects who applied it once a day (on the evening) to the face.

On D14

- The subjects returned to the laboratory; the last application of product was done the evening before.
- The subjects brought back the completed daily log (D0-D13) and the studied product.
- Implementation of a zoomed photograph of the studied zone of forehead.
- Implementation of print with Sifflo® gel on the horizontal lines of forehead.
- Distribution of the new daily log (D14-D27).

On D28

- The subjects returned to the laboratory; the last application of product was done the evening before.
- The subjects brought back the completed daily log (D14-D27) and the studied product.
- Implementation of a zoomed photograph of the studied zone of forehead.
- Implementation of print with Sifflo® gel on the horizontal lines of forehead.
- Measurements of skin biomechanical properties using Cutometer® on the defined temple.
- Distribution of the new daily log (D28-D55).

On D56

- The subjects returned to the laboratory; the last application of product was done the evening before.
- The subjects brought back the completed daily log (D28-D55) and the studied product.
- Implementation of a zoomed photograph of the studied zone of forehead.
- Implementation of print with Sifflo® gel on the horizontal lines of forehead.
- Measurements of skin biomechanical properties using Cutometer® on the defined temple.
- The subjects filled in a subjective evaluation questionnaire.

2.6.2. Adverse Events/Serious Adverse Events

During the study, the following rules were applied:

2.6.2.1. Definitions

An Adverse Event (AE) is defined as any noxious symptom, temporarily linked to the use of a study product, occurring in a subject taking part in a clinical trial, whether or not this symptom is related to the studied product(s).

An adverse reaction is defined as any noxious and unexpected reaction that might be related to the studied product(s).
All adverse events judged, by the investigator, as being possibly, probably or certainly related to the studied product are considered as adverse reactions.

A Serious Adverse Event (SAE) is defined as an adverse event or effect that:
- results in death (note: death is the outcome, not the event),
- is life threatening,
- requires in-patient hospitalization (at least one night) or prolongation of existing hospitalization (does not include hospitalization scheduled before the inclusion),
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- is considered like by the investigator.

The severity/intensity of adverse events can be graded on a three-point scale:
- **Mild** or *Grade 1*: discomfort noted, but does not disturb normal daily activities.
- **Moderate** or *Grade 2*: discomfort sufficient to reduce or affect normal daily activities.
- **Severe** or *Grade 3*: inability to work or have normal daily activities.

2.6.2.2. Documentation

All concomitant treatments are reported in the CRF and the study report.
All Adverse Events likely to be related to the studied product (adverse reactions) are reported in the CRF and the study report.
All Serious Adverse Events are reported in the CRF and the study report.

2.6.2.3. Notification

The investigator declares to the sponsor, by fax or e-mail, the occurrence of adverse reactions according to their severity and their unexpectedness (according to the investigator's advice).

All Serious Adverse Events are transmitted by e-mail to the sponsor without delay, at the latest 24 hours after knowledge of their occurrence.
A SAE declaration form signed by a physician is sent, within 48 hours, by fax or e-mail with acknowledgement of receipt.

2.6.2.4. Follow-up

When an adverse event likely to be linked to the studied product or the protocol persists at the end of the study, the Investigator ensures that the subject is followed up until total resolution of the event or stabilization of the symptoms without taking off the application of the obligations and the responsibilities of the sponsor.

2.6.2.5. Occurrence of pregnancy

The occurrence of a pregnancy (reported or diagnosed) after inclusion in the study is considered as an intercurrent event not related to the studied product(s) nor the protocol and induces the immediate dropping out of the subject.
A follow-up will be done according to the current internal procedures up to the end of the pregnancy or to its interruption.

2.6.2.6. Early termination of the study

♦ **Study exit conditions**

* In compliance with the Helsinki Declaration (1964) and its successive updates and with the French law 2004-806 dated August 9, 2004 concerning public health (ref: 1 to 3 in §8.1), subjects have the right to exit from the study at any time and for any motive.

* The investigator can also interrupt the subject participation in the study prematurely in the case of an intercurrent disease or adverse effect.

* The sponsor can demand that any subject be excluded from the study for major infringements to the protocol, for administrative reasons or any other motive.

Nevertheless, premature removal of a high percentage of subjects from the study can make the study difficult or impossible to interpret. Consequently, any premature exit without valid motives should be avoided as much as possible and is carefully documented in the case report form, the final report and, if necessary, in the Adverse Event form.

Every premature exit must be classified under one of the following headings:
- presence of a non-inclusion criteria,
- Adverse Event occurrence,
- Serious Adverse Event occurrence,
- withdrawal of consent,
- untraceable panelist,
- appearance of non-inclusion criteria,
- non-adherence to the protocol,
- other reason.

♦ **Replacement conditions**

No replacement is foreseen as 10% additional subjects were planned to be included in the study.

2.6.3. Collection and validation of data

According to the law "informatique et libertés" (ref: 4 in §8.1), an identification code was attributed to each subject on purpose to keep his identity confidential. This code consists of: the first three letters of the subject's name and the first two letters of his first name.

The personnel in charge of the study (technician, physician,...) added data to subject case report form and to a computerized data base.
Data were validated by Dermscan's study manager.

2.6.4. Audit and trial monitoring visit

An audit and/or trial monitoring visit might be carried out at the sponsor's request or by the appropriate regulatory authority. The aim of the monitoring visit is to verify that the study is conducted according to the determined protocol and current regulations.

2.6.5. Quality assurance and quality control

In order to ensure the conformity of the clinical trials to the study sponsor's requirement, DERMSCAN has implemented a quality management system which has been certified ISO 9001: 2000 by AFNOR certification.
This quality assurance system includes Good Clinical Practices (GCP) and regulation requirements.

Each study report is the subject of a quality control by a member of the DERMSCAN Proofreading Committee. The proofreader is chosen because he(she) is not involved in the audited study. The inspection of the study report allows to confirm that the results reflect exactly the study raw data.

A certificate of quality control, signed by the person who checked the report is enclosed in each study report to certify that the study report reflects the study raw data and fulfils any standard and regulatory requirements.

2.7. Studied product

2.7.1. Confidentiality procedure

The products supplied by the sponsor were encoded.

2.7.2. Storage

Before the beginning of the study, the products were kept at room temperature in a dedicated air-conditioned room. This room was locked and access controlled.

2.7.3. Reference

Rivoli Night cream Lab-00008.8, Batch #67503.

2.7.4. Aspect

Beige fluid emulsion.

2.7.5. Labeling

Example of labeling of each product by the clinical trial center and translation:

DERMSCAN Etude n°	DERMSCAN Study #
N° vol : ..... En cas d'urgence : n° tél..... N°Dermscan : ..... Conservation : ..... A tenir hors de portée et de la vue des enfants. A utiliser sous stricte surveillance médicale pour essai clinique.	Subject#:..... Emergency telephone number: ..... Dermscan ref.:..... Conservation: ..... Keep out of reach and sight of children. To be used only under strict medical supervision for clinical trial.

2.7.6. Application frequency

Once-daily application, on the evening.

2.7.7. Application site and method

- Application site: to the whole face and particularly on the horizontal lines on forehead
- Application method: under normal conditions of use, by a slight massage until penetration.

2.7.8. Product issue

The products were delivered to the subjects by the technician with an explanation of the application conditions.

2.7.9. Product future

A sample of the studied products will be kept by the laboratory for a period of one year after the sending of the report.
By default, the remaining products will be destroyed according to the current internal procedures.

2.8. Method of product attribution to the subjects

2.8.1. Randomization method for the application zones

The zone of application of the studied product was randomized according to the list presented in **Appendix 9.1.**

2.8.2. Product attribution

Not applicable. All the subjects received the same reference of product.

2.9. Data analysis

2.9.1. Calculation formulas

The raw variations (Δ) and in percentage (Δ%) of the different studied parameters were calculated according to the following formulas:

$$\Delta = (TZ_{ti} - TZ_{t0})$$

$$\Delta\% = \frac{(TZ_{ti} - TZt0)}{TZ_{t0}} \times 100$$

with:
TZ: value obtained on the treated zones
t0: before application
ti: at each measurement time after application

Remarks:

The percentage of the variation (Δ%) is expressed in percentage of the variation on the measurement's zone (TZ_{ti} - TZ_{t0}). These variations are balanced at the initial value TZ_{t0} (before application).

This expression (Δ%), therefore, gives the variation, in percentage, on the measurement's zone compared to the initial conditions (TZ_{t0}).

Measured values are presented in raw value tables. These tables also show the descriptive statistics: means, medians, minima, maxima, standard errors of the means (SEM) and confidence intervals of 95% (95% CI).

Also, raw variations, percentage variations, descriptive statistics and the results of the statistical analysis (p) are presented in the variation tables.

2.9.2. Statistical method

The statistical analysis determined the significance of the measurement variations obtained under the effect of the studied product.

The comparison was on the values obtained before and at the different times of kinetics after treatment.

Data were analyzed with a **paired t-test**. This method tests whether the mean of sample differences between pairs of data is significantly different from the hypothetical mean, zero under the null hypothesis (H0).

The alternative hypothesis (H1) was that the average difference was either greater or less than 0 (two-tailed test). Before carrying out a test, a type I error of 5% is chosen (which corresponds to the risk of rejecting a true null hypothesis).

→ **If p≤0.05**, H0 was rejected. There was a significant difference between before and after the treatment.
→ **If p>0.05**, H0 was accepted, the mean was not different from 0. Data did not show a significant difference between before and after the treatment.

2.9.3. Statistical software

The software used was EXCEL 9.0 version 2003.

2.10. Archives

Data will be securely archived digitally and on paper for ten years from the date of dispatch of the final report. At the end of this period, the study archives will be destroyed unless otherwise stipulated in writing by the sponsor.

All the documents relating to this study are archived during one year maximum at Dermscan before being sent to the company LOCARCHIVES (Parc industriel de la plaine de l'Ain – Allée des cèdres – 01150 SAINT-VULBAS – FRANCE).

Study follow-up

Subjects characteristics

Results

3. STUDY FOLLOW-UP

3.1. Population

	Number of subjects			Reason(s)	
	Included subjects	**Subjects who completed the study**	**Analyzed subjects**	**Subjects who did not complete the study**	**Non-analyzed subjects**
Quantirides® Macrophotogaphs	*21*	*21 on D14* *21 on D28* *20 on D56*	*21 on D14* *20 on D28* *20 on D56*	*Subject #11: untraceable on D56.*	*Subject #7: print problem on D28.*
Cutometer®	*21*	*21 on D28* *20 on D56*	*21 on D28* *20 on D56*		/
Subjective evaluation questionnaire	*21*	*20 on D56*	*20 on D56*		/

3.2. Protocol non-adherences

Description of the non-adherence	***Type of non-adherence*** *(minor / major)*	***Data kept in the analysis*** *(yes / no)*
Subject #4 did not apply the product on D8, D21 and D22.	*minor*	*yes*
Subject #18 did not apply the product on D30 and D47.	*minor*	*yes*

The protocol non-adherence of subjects #4 and #18 did not invalidate the data obtained for these subjects.

3.3. Audit / Trial monitoring visit

No monitoring visit took place.

4. SUBJECT CHARACTERISTICS

The table below presents the observations concerning the subjects included in the study.

Subject	Last name	First name	Age	Sex	Medical events or treatments occurred during the study	Comments	Inclusion date	End date
1	FEV	MI	61	F	Doliprane® on October 15, 2009.	None	September 25, 2009	November 19, 2009
2	TSC	DA	61	F	None	None	September 25, 2009	November 19, 2009
3	DON	CO	57	F	None	None	September 25, 2009	November 19, 2009
4	GRA	VE	42	F	Efferalgan® on November 12, 2009.	None	September 25, 2009	November 19, 2009
5	ANN	DA	60	F	None	None	September 25, 2009	November 19, 2009
6	AGA	PA	51	F	None	None	September 25, 2009	November 19, 2009
7	MOU	YV	61	F	None	None	September 25, 2009	November 19, 2009
8	MEB	AN	61	F	None	None	September 25, 2009	November 19, 2009
9	BOS	CH	58	F	None	None	September 25, 2009	November 19, 2009
10	LAS	AN	51	F	None	None	September 25, 2009	November 19, 2009
11	GAR	MO	61	F	None	Untraceable on D56	September 25, 2009	October 23, 2009
12	BUS	JO	59	F	None	None	September 25, 2009	November 19, 2009
13	AUZ	FE	63	F	None	None	September 25, 2009	November 19, 2009
14	VIT	AG	52	F	None	None	September 25, 2009	November 19, 2009
15	KAM	EL	49	F	None	None	September 25, 2009	November 19, 2009
16	ROY	BE	57	F	Aspirine® on October 3, 6, 12, 18, 2009 and November 1 and 10, 2009.	None	September 25, 2009	November 19, 2009
17	PIC	CH	44	F	None	None	September 25, 2009	November 19, 2009
18	MON	MA	47	F	None	None	September 25, 2009	November 19, 2009
19	DEV	VI	54	F	None	None	September 25, 2009	November 19, 2009
20	FOR	PA	55	F	None	None	September 25, 2009	November 19, 2009
21	HUS	TH	64	F	None	None	September 25, 2009	November 19, 2009

Mean	**56**	**F**	21
Median	57	**M**	0
Minimum	*42*		
Maximum	*64*		
SEM	**1**		
95% CI	3		

Legend: F: female
M: male

5. RESULTS

5.1. Anti-wrinkle effect

5.1.1. Results synthesis

Individual results are presented in **Appendix 9.2**.

The studied parameters are:
- **micro-relief furrows** (number and depth),
- **medium wrinkles** (number and depth),
- **deep wrinkles** (number and depth),
- the **total wrinkled surface** (mm²).

- A **decrease in the number and/or the depth of the micro-relief furrows** (without variations of the other parameters) characterizes a **smoothing effect** of the product.
- An **increase in the number of the micro-relief furrows with a decrease in the other parameters** characterizes an **anti-wrinkle effect** of the product.
- A **decrease in all the parameters** characterizes **a smoothing** and an **anti-wrinkle effect** of the product.

A synthesis is presented below.

Variations of cutaneous relief parameters in comparison with the initial state

				Student t-test		
		Δ (mean ± SEM)	Δ% on mean	p	significant	% of subjects with the expected effect
Number of microrelief furrows	D14 - D0	+2 ± 2	+12%	0.371	No	43%
	D28 - D0	+1 ± 2	+12%	0.470	No	35%
	D56 - D0	+3 ± 2	+25%	0.187	No	35%
Depth of microrelief furrows (µm)	D14 - D0	-0.8 ± 0.9	-2%	0.345	No	62%
	D28 - D0	+1 ± 1	+1%	0.341	No	45%
	D56 - D0	-0.3 ± 0.6	+0%	0.642	No	60%
Number of medium wrinkles	D14 - D0	-4 ± 3	-15%	0.141	No	67%
	D28 - D0	-1 ± 3	-0%	0.855	No	45%
	D56 - D0	**-8 ± 3**	**-28%**	**0.036**	**Yes**	**65%**
Depth of medium wrinkles (µm)	D14 - D0	-1.2 ± 1.5	-2%	0.443	No	62%
	D28 - D0	-0.8 ± 1.4	-1%	0.608	No	55%
	D56 - D0	-0.7 ± 1.4	-1%	0.629	No	60%
Number of deep wrinkles	D14 - D0	**-3 ± 1**	**-37%**	**0.004**	**Yes**	**67%**
	D28 - D0	-1 ± 1	-14%	0.208	No	60%
	D56 - D0	**-3 ± 1**	**-38%**	**0.003**	**Yes**	**75%**
Depth of deep wrinkles (µm)	D14 - D0	**-10.2 ± 5.8**	**-6%**	**0.098**	**Limit**	**70%**
	D28 - D0	-0.8 ± 6.5	+0%	0.906	No	47%
	D56 - D0	-7.5 ± 6.7	-4%	0.283	No	59%
Total wrinkled surface (mm²)	D14 - D0	**-3.8 ± 1.3**	**-40%**	**0.010**	**Yes**	**81%**
	D28 - D0	-2.0 ± 1.4	-18%	0.174	No	60%
	D56 - D0	-1.8 ± 1.5	-27%	0.230	No	75%

In comparison with the initial state, product "Rivoli Night cream Lab-00008.8 batch #67503":

- **induced after 14 days:**
  - **a significant decrease in the number of deep wrinkles (-37% in average),**
  - **a decrease, limit in significance, in the depth of deep wrinkles (-6% in average)**
  - **a significant decrease in the total wrinkled surface (-40% in average).**

  These decreases were observed in respectively 67%, 70% and 81% of the subjects.
- **after 28 days, did not induce any relevant variation of the cutaneous relief parameters.**
- **induced after 56 days:**
  - **a significant decrease in the number of medium wrinkles (-28% in average),**
  - **a significant decrease in the number of deep wrinkles (-38% in average),**

  These decreases were observed in respectively 65% and 75% of the subjects.

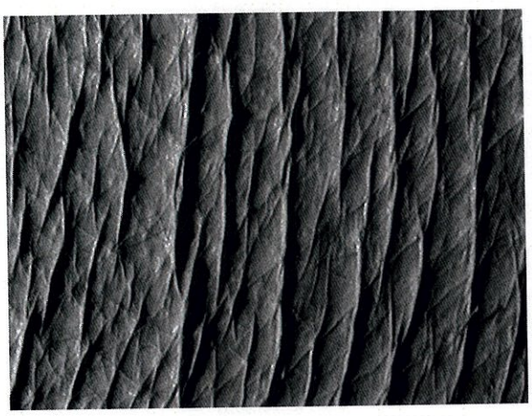
Results obtained characterize a significant anti-wrinkle efficacy of product from 14 days of use.

5.1.2. Illustrations

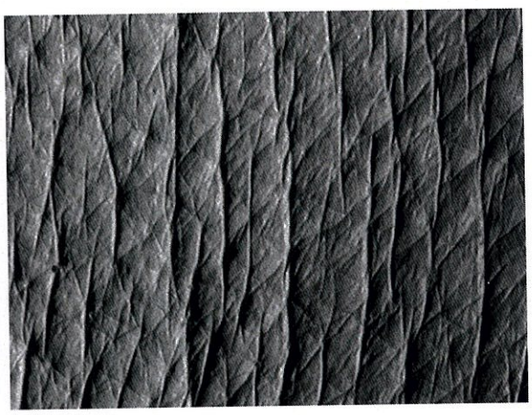
An example of results obtained with product "Rivoli Night cream Lab-00008.8 batch #67503" is presented below, for subject #3, who presents the best visual result observed.

Subject #3

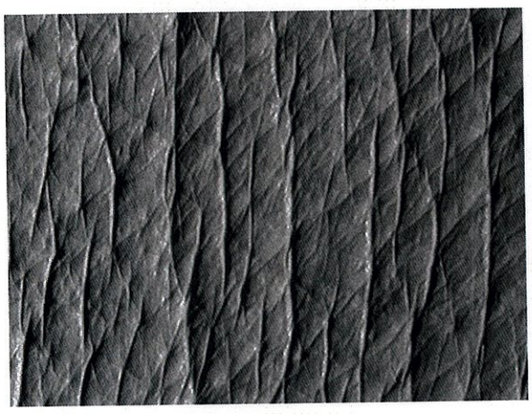
ON D0



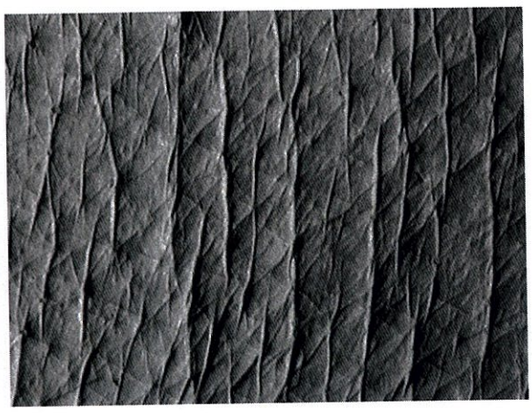
On D28



On D14



On D56



5.2. Firming effect

Individual results are presented in **Appendix 9.3.**

- an **increase in immediate elongation (ΔUe)** characterizes an **improvement in skin suppleness**.
- a **decrease in total elongation (ΔUf)** characterizes a **tensing effect** of the product (ie an increase in (-ΔUf)),
- a **decrease in residual elongation (ΔX)** characterizes a **tonic effect** of the product (ie an increase in (-ΔX)),
- an **increase in the immediate retraction/total elongation ratio** characterizes a **firming effect** of the product (ie increase in (ΔUr/Uf)).

A synthesis of the results is presented below.

Variations of the skin biomechanical properties in comparison with the initial state

	Kinetics	Δ in mm (mean ± SEM)	Variation in % on the mean	Student t-test		% of subjects with the expected effect
				p=	significance	
Suppleness (ΔUe)	D28 - D0	0.007 ± 0.009	3%	0.462	No	33%
	D56 - D0	-0.001 ± 0.013	0%	0.949	No	35%
Tension (-ΔUf)	D28 - D0	-0.009 ± -0.009	-3%	0.331	No	33%
	D56 - D0	-0.001 ± -0.013	0%	0.921	No	50%
Tonicity (-ΔX)	D28 - D0	-0.009 ± -0.009	-5%	0.316	No	33%
	D56 - D0	-0.007 ± -0.010	-4%	0.514	No	40%
Firmness (ΔUr/Uf)	D28 - D0	-0.008 ± 0.018	-2%	0.655	No	43%
	D56 - D0	-0.020 ± 0.017	-6%	0.276	No	35%

Under these study conditions, after 28 and 56 days of once-daily use, product "Rivoli Night cream Lab-00008.8, Batch #67503" did not induce any relevant variation of the cutaneous biomechanical properties.

5.3. Subjective evaluation questionnaire

The subjects' answers (in percentage) to the subjective evaluation questionnaire are presented in **Appendix 9.4**.

To be easier to read, the percentages were rounded off. The sum of these percentages may be different from 100%.
In this study (n=20), one subject represents 5.0%.

The synthesis of the answers is presented in the table below.

GLOBAL APPRECIATION AND ORGANOLEPTIC CHARACTERISTICS OF THE PRODUCT	
Global appreciation	**75%**
very pleasant	45%
pleasant	30%
Aspect	**90%**
very pleasant	30%
pleasant	60%
Texture	**85%**
very pleasant	40%
pleasant	45%
Fragrance	**55%**
very pleasant	15%
pleasant	40%
Easy spreading	**95%**
very easy	60%
easy	35%
Easy penetration	**90%**
very easy	40%
easy	50%
Immediate tensor/lifting effect	**90%**
important	15%
moderate	65%
slight	10%
Immediate freshness sensation	**85%**
important	25%
moderate	35%
slight	25%

D56: PRODUCT EFFICACY	
Global improvement in the skin state and aspect	**90%**
very important	5%
important	30%
moderate	35%
slight	20%
Wrinkles and fines lines smoothed	**45%**
much more	5%
more	40%
Appeased skin- relieved congestion	**70%**
much more	5%
more	65%
Signs of tiredness attenuated	**65%**
much more	5%
more	60%
Moisturized skin	**80%**
much more	10%
more	70%
Firm skin	**45%**
much more	5%
more	40%
Younger skin	**55%**
Decrease in the number and depth of wrinkles	**45%**
much less wrinkled	0%
less wrinkled	45%
Anti-wrinkle efficacy	**50%**
very efficient	10%
efficient	40%
PRODUCT TOLERANCE	
Unpleasant or uncomfortable sensation	**5%**

Subject #07 felt itching and dryness from D44 to D55 with pimples at the lower part of the cheek.

FUTURE USE OF THE PRODUCT	
Would continue to use the product	**55%**
Would change the currently used cosmetics with this one	**50%**
Would buy the product	**60%**
very certainly	15%
certainly	35%
perhaps	10%

Laboratoire Dermscan

Conclusion

Certification

Bibliography

6. CONCLUSION

This study had as primary objectives to evaluate the anti-wrinkle and firming effects, after 14, 28 and 56 days of use of product "Rivoli Night cream Lab-00008.8, Batch #67503".

The secondary objectives of this study were, for the studied product:

- to evaluate the subjective appreciation of its organoleptic characteristics, its efficacy, its tolerance and its future use,
- to illustrate its visual expected effect.

Study conditions:

Product	**Reference:** Rivoli Night cream Lab-00008.8, Batch 67503.	**Galenic form:** Beige fluid emulsion.	
Experimental plan	Open and intra-individual study.		
Assessment criteria	-Analysis of the cutaneous relief parameters using Skin Image Analyser® and Quantirides® software. -Illustration of the visual expected effect by macrophotographs.	**Kinetics**	D0-D14-D28-D56.
		Methodology	Before / After.
		Measurement zone	Forehead.
		Application frequency	Once- daily (on the evening).
	-Analysis of the skin biomechanical properties using Cutometer®.	**Kinetics**	D0-D28-D56.
		Methodology	Before / After.
		Measurement zone	Temples.
		Application frequency	Once- daily (on the evening).
	-Subjective evaluation using questionnaire.	**Kinetics**	D56.
		Methodology	Before / After.
		Measurement zone	Face
		Application frequency	Once- daily (on the evening).
Studied population	Number of subjects analyzed: -21 on D0 and D28 and 20 on D56 for firming effect and macrophotographs, -21 on D0 and D14 and 20 on D28 and D56 for anti-wrinkle effect ; -20 for subjective evaluation questionnaire.		
	Average age: 56±1 years (between 42 and 64 years old).		
	Main inclusion criteria: • Sex: female. • Age: between 35 and 65 years old. • Subject having wrinkles on the forehead.		

Under these study conditions, product "Rivoli Night cream Lab-00008.8, Batch #67503":

- **induced a <u>significant anti-wrinkle effect from 14 days of use</u>, characterized by;**
  - **a significant decrease in the number of deep wrinkles of -37% on average, decrease observed in 67% of subjects;**
  - **a decrease, limit in significance in the depth of deep wrinkles of -6% on average, decrease observed in 70% of subjects;**
  - **a significant decrease in the total wrinkled surface of -40% on average, decrease observed in 81% of subjects;**

  <u>This effect was again measured after 56 days of use</u>, with:
  - **a significant decrease in the number of medium wrinkles of -28% on average, decrease observed in 65% of subjects;**
  - **a significant decrease in the number of deep wrinkles of -38% on average, decrease observed in 75% of subjects;**

- **did not modify on average skin biomechanical properties;**

- **satisfied a majority of the subjects for:**
  - **its <u>organoleptic characteristics</u>: pleasant aspect (90%) and texture (85%), easy spreading (95%) and penetration (90%);**
  - **<u>its immediate efficacy</u>: tensor/lifting effect (90%) and freshness sensation (85%);**
  - **<u>its efficacy 56 days after application</u>: 90% of the subjects noticed a global improvement in the skin state and aspect, 70% found their skin appeased, relieved congestion, 65% found their signs of tiredness attenuated and 80% found their skin more moisturized.**

55% of the subjects would continue to use this product and 60% of the subjects would buy it.

7. CERTIFICATION

The study was conducted according to Helsinki Declaration (1964) and its successive updates. Data were obtained using the study protocol, current internal procedures and in the spirit of the note for guidance on Good Clinical Practice CPMP / ICH / 135 / 95, January 1997 (ref: 1 to 4 in §8.1).

Only the hard copy of the report (color bands) transmitted by Dermscan can be considered as the original and official document. Digitally-produced or electronic documents transmitted by Dermscan are not protected by an electronic signature, according to Law n°2000-230 dates March 13, 2000 and its applicable decrees. The contents of digitally-produced or electronic documents in no means engage the responsibility of Dermscan.
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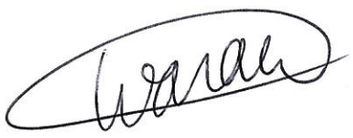
This study was totally performed under the responsibility of Dermscan.

Dermscan quality system is certified ISO 9001: 2000.

All the observations and numerical data collected throughout the study are reported in this document. We certify that these data are in accordance with the obtained results.

Date and signature: December 7, 2009

Name Function	**Carine KURDIAN** Trial Manager Assistant	**Hagira WARAY** Research Technician



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