Clinical Study Report

EVALUATION OF TOLERABILITY AND EFFICACY OF THE CRISTAL CRYOLIPOLYSIS TREATMENT ON THE LOCALIZED FAT DEPOSITS IN OBESE SUBJECTS

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Sponsor code NA

Sponsor

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1 TITLE PAGE

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Twenty (20) obese subjects</td></tr>
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Frederic SAMSON, CEO</td><td>Principal Investigator (name and affiliation)
Pr. Thierry PASSERON, MD, PhD</td></tr>
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This study was performed in compliance with Good Clinical Practice (GCP) including the archiving of essential study documents.

REPORT APPROVALS

Sponsor approval

The following person has approved this Clinical Study Report on behalf of DELEO SAS, by manually signing below:

Frédéric SAMSON
CEO DELEO SAS

Signature: *Date:*

Investigators approval

The following persons have approved this Clinical Study Report:

Pr. Thierry PASSERON, MD, PhD
Principal Investigator

Signature: *Date:*

Dr. Abdallah KHEMIS, MD
Investigator Coordinator

Signature: *Date:*

2 SYNOPSIS

Name of Sponsor	DELEO SAS
Title of Study	**EVALUATION OF TOLERABILITY AND EFFICACY OF THE CRISTAL CRYOLIPOLYSIS TREATMENT ON THE LOCALIZED FAT DEPOSITS IN OBESE SUBJECTS**
Investigator(s)	Pr. Thierry PASSERON, MD, PhD, Principal Investigator Dr. Abdallah KHEMIS, MD, Investigator Coordinator Pr. Jean Philippe LACOUR, MD, PhD, co-investigator Pr. Patrick FENICHEL, MD, co-Investigator
Study Center(s)	Dermatology Department Hôpital L'Archet 2 151, route de Saint Antoine de Ginestière 06202 Nice Cedex 3 France
Publication(s)	NA
Study period Date of First Enrollment: 15-Jul-2016 Date of Last Completed: 27-Sep-2016	**Phase of development** Medical Device

Study Objectives

Primary objective:

- The primary objective of this trial was to reduce from at least 30% the greasy fold thickness after 2 months of the Cristal Cryolipolysis treatment using a caliper tool measurement.

Secondary objective:

- To assess the safety and tolerability of the Cristal Cryolipolysis treatment in the study
- To assess the satisfaction of patient with regards to efficacy and tolerability of the treatment.
- To assess the effects of LED light after Cristal Cryolipolysis treatment.

Study Design

Open study with intra-individual comparisons.

The study consisted of a selection visit followed by three experimental visits (Day0, T1 month, T2month).

Number of Subjects (planned and analyzed)

Twenty (20) obese subjects

Diagnosis and Main Criteria for Inclusion

- Adults, men and women (≥18 to 65 years of age) with a BMI between 30 and 35.
- Greasy fold thickness between 2 -15 cm (measure performed by caliper)
- Stable weight without changes within the 6 months prior to the study and remaining stable during the study.

Test device description

The Cryolipolysis Cristal is a class IIa medical device which consists to apply a controlled cooling on the fat deposits located on the body. Cooling is generated by an effect Peltier device.
The Cryolipolysis Cristal is dedicated to treat the located pocket of fat. It allows to improve the skin texture and significantly reduces the located fat layers. It is equipped with two handpieces allowing to treat simultaneously two areas.
This medical device is intended for doctor's offices; it has a EC marking following the 93/42/CEE directive.

Duration of Treatment

1 hour

Study Efficacy Endpoints

- **Primary Endpoint(s)**

Measure of the greasy fold thickness using the caliper at each visit

- **Secondary Endpoint(s)**

The secondary endpoints were the followings:

- Measure of the subcutaneous fat thickness by echography (at V2, V3 and V4)
- Measure of skin biomechanics (elasticity) using the Cutometer (at V2, V3 and V4)
- Measure of the target area using standardized photographs (at V2, V3 and V4)
- Measure of the glycaemia and lipids status at each visit.
- Measure of the patient satisfaction (at V3 and V4)

Principal Statistical Methods

The principal criterion is the greasy fold thickness after 2 months of treatment. The comparison T2month versus baseline was performed using a Student t test for paired data.

The objective to obtain a reduction of at least 30% of the greasy fold thickness was checked by the calculation of the 95% interval of confidence of the mean reduction of the thickness at T2month. The reduction of 30% had to be comprised within this interval of confidence.

Summary of Results

- **Subject Population**

Twenty obese subjects were included and completed the study. Most subjects were females (75%). At Screening, the mean age of the subjects was 45 years (from 28 to 65 years).

- **Efficacy Results**
  - **Primary Endpoint(s)**

The greasy fold thickness decreased whatever the post-treatment with LED or not. Compared to the Screening visit, the greasy fold thickness was significantly reduced at T1month and T2month. The primary endpoint was reached at T2month because the expected percentage of 30% reduction was observed.

  - **Secondary Endpoint(s)**

The subcutaneous fat thickness, measured by echography, decreased whatever the post-treatment with LED or not. Compared to the Before treatment value, the subcutaneous fat thickness was significantly reduced at T1month and T2month. At T2month, the reduction of subcutaneous fat thickness measured by echography was about -24%.

Concerning biomechanical properties of the skin, the results indicated that the Cristal Cryolipolysis procedure did not affect the skin firmness and even slightly improve the skin elasticity at T2month for both types of zones.

- **Safety Results**

Safety results showed a better tolerance on LED treated zone which displayed lower scores of erythema and edema following treatment procedure. Fifty-five percent (55%) of subjects did not feel any painful post-procedure reactions and the mean duration of pain was 5 days for subjects experiencing pain.

Concerning blood lipids, a decrease of blood cholesterol total, LDL and HDL was observed at T1month with normal level recovery at T2month. For the hormonal blood status, a decrease of Free T4 and an increase of Free T3 were measured at T1month with normal level recovery at T2month. No significant variations of TSH and no changes in glycaemia were measured during the study.

Two adverse events were reported. One AE concerned a pregnancy revealed by the pregnancy test of the last visit and was judged as non-related to the study content. The second AE was a severe local urticaria-like reaction observe just after the Cristal procedure (cold urticaria, AE related to treatment) and resolved within a few hours.

There was no sign of aggravation in patients with stretch marks.

Conclusion

In the conditions of this study, the Cristal Cryolipolysis treatment was found efficient and safe to treat the subcutaneous fat deposits in obese patients.

Date of Report

25 April 2017

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

AE	Adverse Event
ANSM	French National Competent Authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé)
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organisation
D	Day
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IUD	Intra-Uterine Device
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
N	Number of Subjects
NA	Not Applicable
p	p-value
PP	Per Protocol
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
T	Temperature

Units

bpm	*beats per minutes*
cm²	*centimeter square*
g	*gram*
h	*hour*
kg	*kilogram*
m²	*meter square*
mg	*milligram*
ml	*milliliter*
mm	*millimeter*

5 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study protocol, all amendments, and any other advertised or written information about the study provided to subjects, were reviewed and approved by an appropriate Ethics Committee (Comité de Protection des Personnes (CPP) Sud Méditerranée V Nice 06-France) on 7 December 2015.

A complete dossier comprising the study documents was sent to the French Competent Authority, the Agence Nationale de Sécurité du Médicament (ANSM), which gave its authorization on 20 November 2016.

5.2 ETHICAL CONDUCT OF THE STUDY

This study was conducted in accordance with the ethical principles initially outlined in the Declaration of Helsinki and Good Clinical Practice (GCP), and complies with local regulatory requirements as written at the time of the study initiation.

5.3 SUBJECT INFORMATION AND INFORMED CONSENT

All subjects who participated in this clinical trial were required to be fully informed about the clinical trial in accordance with GCPs guidelines and guidelines and in accordance with local requirements.

Prior to inclusion in the clinical trial, the subject had to sign and date the Informed Consent Form (ICF). The Investigator was responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject with a copy of the signed and dated consent form(s).

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

One Investigational Center in Nice, France participated in the study.

Investigator team

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DELEO SAS was the Sponsor

Sponsor representatives

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7 INTRODUCTION

7.1 STUDY RATIONALE

In France, the obesity reaches about 10% of the adult population and the overweight affects 30% of adults.

The obesity is a disease because it alters the health. That is the excess of fat mass which produces the development of various diseases (diabetes, hypertension, sleep apnea, etc…). The fat mass is estimated from the calculation of the Body mass index (BMI) which takes into account the weight and the size.

The BMI calculation is the following: $BMI = \frac{\text{Weight (kg)}}{(\text{Size in meter})^2}$

A BMI between 25 and 30 corresponds to an overweight. The obesity begins at BMI equal to 30. These values are not valid for children and elderly subjects (above 70 years).

The measure of the waist size allows to identify an excess of fat on the belly. When the waist size is greater than 90cm for women (outside of pregnancy) and over 100cm for men, one can consider an abdominal obesity. A gynoid obesity is considered when the excess of fat is mainly located on the thighs as it can be observed in women (« jodhpurs aspect »). An android obesity is considered when the excess of fat is mainly located on the belly (equivalent to abdominal obesity).

The more the BMI is high, the more the risk of having health problems increases.

The health alterations due to obesity may take several forms:

- Physical: diabetes, hypertension, hypertriglyceridemia, cardiovascular diseases, sleep apnea, etc…
- Psychological: depression, etc…
- Social: discrimination, isolation, etc….

The expected benefit is the destruction of the adipocytes by the effect of cooling which induces the reduction of located fat mass. The Cristal Cryolipolysis allows to decrease the fat mass at the level of the abdomen, the tights (« jodhpurs aspect »), the back, under the arms, etc….

In the long term, the treatment could be repeated several times in order to treat several areas or to improve the results on a same area. This was not performed in the study.

The Cryolipolysis technology exists since a decade. Numerous published articles have demonstrated its efficacy and safety on non-obese population (see 14).

The Cristal Cryolipolysis was never tested in clinical investigations on patients. Therefore, we have based our investigation on the existing clinical studies of our concurrent whose devices are equivalent to our system. Our medical device Cristal Cryolipolysis has numerous similitudes of use with the other existing Cryolipolysis devices.

7.2 BENEFIT/RISKS ASSESSMENT

The expected clinical benefit was the destruction of adipocytes by the cooling effect which induces the reduction of fat masses in obese subjects. The adipocytes having undergone an apoptosis by the cold effect are eliminated by the natural ways.

The treatment by Cristal has to allow the improvements of the obesity symptoms by diminishing the fat masses. A blood sampling follow-up as performed in order to compare the glycaemia and the lipids status before and after treatment.

Thanks to a simple and non-invasive technique (the Cryolipolysis), the interest is to improve the health conditions of obese patients on the physical, psychological and social aspects.

The expected and predictable side effects are the following:

-Intense tightness, pains, cramps at the beginning of the treatment. These sensations stop generally during the dullness by the cooling effect on the treated zone.

- The treated zone can present a temporary stiff aspect following the treatment. A temporary whitening of the skin can be observed.

- Risk of nausea and vertigo during the treatment. These reactions disappear generally in a few minutes.

- Bruises, oedema, sensibility, redness of the skin at the level of the treated area can persist several hours after the care.

- A loss of sensibility, strong itches, pains, tingling or dullness, strong cramps and painful muscular contractions can appear at the level of the zone handled during several weeks after the treatment.

More important side effects can be observed. Indeed rarely, vasovagal episode, burns, skin brown coloration, rigidity and hypoesthesia or the deformation of the treated area can appear. No serious adverse events were expected.

The risks analysis was performed according to the ISO 14971 standard. The residual risks were judged acceptable on the basis of the “risks acceptability criteria”. Indeed, these risks were under control after implementation of corrective actions. According to the ISO 14971 standard, the Benefit/Risks ratio has to be analyzed if the residual risks are judged inacceptable on the basis of the “risks acceptability criteria”. The residual risks being under control, the Benefit/Risks ratio of the study was thus judged to be favourable.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this trial was to reduce from at least 30% the greasy fold thickness after 2 months of the Cristal Cryolipolysis treatment using a caliper tool measurement.

8.2 SECONDARY OBJECTIVE

- To assess the safety and tolerability of the Cristal Cryolipolysis treatment in the study
- To assess the satisfaction of patient with regards to efficacy and tolerability of the treatment.
- To assess the effects of LED light after Cristal Cryolipolysis treatment.

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN DESCRIPTION

Open study, monocentric with intra-individual comparisons. The study Flow-chart is described in Table 1 below:

9.1.1 Study Flow Chart

Table 1 Study Design and Schedule of Assessments

STUDY PROCEDURES	**Screening/Inclusion**	**Treatment**	**Evaluations/follow-up**	
Visits	**Visit 1** (1 week maximum before treatment)	**Visit 2 : Day0**	**Visit3 Day28**	**Visit4 Day56**
Informed Consent / Inclusion / non-inclusion criteria	X	X		
Medical history/Concomitant treatments	X			
Demographic Data/ size, weight, BMI Waist size, Hip size, Thigh circumference, chest size	X			
Arterial pressure, heart beating, Temp., ECG	X	X	X	X
Fasting blood sampling, urinalysis, Pregnancy test	X	X	X	X
Measure of the greasy fold thickness of target areas using caliper	X	X	X	X
Dermatological Examination of target areas	X	X	X	X
Areas assessment by the Investigator		X	X	X
Photographs of whole body and target areas		X	X	X
Echographies of Target areas		X	X	X
Elasticity measurement of target areas (cutometer)		X	X	X
Cryolipolysis Cristal procedure		X	X	X
LED Medisol lamp exposure on half of the treated areas		X		
Evaluation of tolerance by the patient (pain, burning, fatigue)		X	X	X

9.1.2 Study Phases

The study consisted of a screening visit followed by three experimental visits (Day 0, Day 28 and Day 56). It was performed as follows:

Screening Visit 1 (Day -7 to Day -2)

The screening visit was performed within 1 weeks before Day 0. Before any study procedure, the subjects received the necessary written and verbal information including informed consent form. Eligibility was determined by physical examination and confirmation of all inclusion/non-inclusion criteria.

The physician examined the patients and performed the following assessments and collected the following information:

- Signature of the informed consent form by the patient,

- Validation of all inclusion/non-inclusion criteria,

- Demographic data: birthday, initials, sex…

- General examination: size, weight, BMI, arterial pressure, heart beat, temperature, waist size, hip size, thigh circumference, chest size

- Dermatologic examination of zones to be treated: normal/abnormal.

- Status of zones to be treated: pigmentation troubles, elasticity, etc…

- Electrocardiogram

- Fasting blood sampling (40mL):

  - Haematology: numeration, blood formula, platelets.
  - Immunology : cryoglobulinemia
  - Biochemistry : glucose, glycated haemoglobin, urea, creatinine, Total and conjugated bilirubin, ALAT, ASAT, GGT, LDH, Calcium, chlorides, potassium, bicarbonate, phosphates, albumin, uric acid, alkaline phosphatase, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides
  - Hormonology : TSH, free T4, free T3

- Urinalysis (with pregnancy test if needed),

- Identification of zones to be treated (area, tracing)

- Measure the greasy fold thickness of zones to be treated using the caliper

- Medical/chirurgical histories

- Concomitant therapies

- Alimentary diet

- Stable weight

Visit 2, treatment (Day0)

- Validation of all inclusion/non-inclusion criteria,

- General examination: size, weight, BMI, arterial pressure, heart beat, temperature, waist size, hip size, thigh circumference, chest size

- Status of zones to be treated: pigmentation troubles, elasticity, etc…

- Photographs of whole body and target zones

- Measure the greasy fold thickness of zones to be treated using the caliper

- Cutaneous echography of the zones to be treated (before/after treatment procedure)

- Elasticity measurements of the target zones before/after treatment procedure

- Urinalysis (with pregnancy test if needed),

- Fasting blood sampling (25mL):

  - Haematology: numeration, blood formula, platelets.
  - Immunology : cryoglobulinemia
  - Biochemistry : glucose, glycated haemoglobin, urea, creatinine, Total and conjugated bilirubin, ALAT, ASAT, GGT, LDH, Calcium, chlorides, potassium, bicarbonate, phosphates, albumin, uric acid, alkaline phosphatase, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides
  - Hormonology : TSH, free T4, free T3

- Modification of the alimentary diet since the last visit: Yes / No

- On going medical treatments

- Procedure Cryolipolysis = treatment (see § 9.3)

- Post-procedure massage

- Exposure with the LED lamp for half of the treated zones

- Evaluations of the patient after procedure: pain / burning / fatigue

- Evaluations physician 30 minutes after procedure: bruising, erythema, oedema, etc.

Visit 3, follow-up (Day28)

- General examination: size, weight, BMI, arterial pressure, heart beat, temperature, waist size, hip size, thigh circumference, chest size

- Photographs of whole body and target zones

- Measure the greasy fold thickness of target zones using the caliper

- Cutaneous echography of the target zones

- Elasticity measurements of the target zones

- Urinalysis (with pregnancy test if needed),

- Fasting blood sampling (25mL):

  - Haematology: numeration, blood formula, platelets.
  - Immunology : cryoglobulinemia
  - Biochemistry : glucose, glycated haemoglobin, urea, creatinine, Total and conjugated bilirubin, ALAT, ASAT, GGT, LDH, Calcium, chlorides, potassium, bicarbonate, phosphates, albumin, uric acid, alkaline phosphatase, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides
  - Hormonology : TSH, free T4, free T3

- Modification of the alimentary diet since the last visit: Yes / No

- Evaluations of the patient: pain / burning / fatigue

- Evaluations physician: bruising, erythema, oedema, etc.

- Assessment of healing (pigmentary troubles, elasticity…)

- On going medical treatments

Visit 4, follow-up (Day56)

- General examination: size, weight, BMI, arterial pressure, heart beat, temperature, waist size, hip size, thigh circumference, chest size

- Photographs of whole body and target zones

- Measure the greasy fold thickness of target zones using the caliper

- Cutaneous echography of the target zones

- Elasticity measurements of the target zones

- Urinalysis (with pregnancy test if needed),

- Fasting blood sampling (25mL):

  - Haematology: numeration, blood formula, platelets.
  - Immunology : cryoglobulinemia
  - Biochemistry : glucose, glycated haemoglobin, urea, creatinine, Total and conjugated bilirubin, ALAT, ASAT, GGT, LDH, Calcium, chlorides, potassium, bicarbonate, phosphates, albumin, uric acid, alkaline phosphatase, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides
  - hormonology : TSH, free T4, free T3

- Modification of the alimentary diet since the last visit: Yes / No

- Evaluations of the patient: pain / burning / fatigue

- Evaluations physician: bruising, erythema, oedema, etc.

- Assessment of healing (pigmentary troubles, elasticity…)

- On going medical treatments

- End of study

9.2 SELECTION OF STUDY POPULATION

Twenty (20) obese subjects had to be included in the study.

9.2.1 Inclusion Criteria

1. Adults, men and women (≥18 to 65 years of age) with a BMI between 30 and 35.
2. Greasy fold thickness between 2 -15 cm (measure performed using the caliper)
3. Stable weight without changes within the 6 months prior to the study and remaining stable during the study.
4. Phototype I to V.
5. Subject must accept to not be exposed to Sun/UV light during the study.
6. Subject must accept to not participate in other clinical trials during the study.
7. Subject must accept recording skin appearance by photography (whole body pictures and located pictures).
8. Patients must be able to understand and communicate with the Investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any

study related activity is performed. Where relevant, a legal representative will also sign the ICF according to local laws and regulations.

9. Patient must be insured under the French social security system.

9.2.2 Non-inclusion Criteria

1. Hospitalization or major surgery performed within 1 month prior to the study or planned during the study.
2. Use of any anti-coagulant or any antalgic within the 24h before Cristal Cryolipolysis treatment.
3. Liposuction procedure within the last 6 months.
4. Subject presenting one of the following contraindications:
   - Cancer on area's treatment
   - Infections localized or general
   - Uncontrolled Diabetes (glycated hemoglobin >7% of total hemoglobin)
   - Uncontrolled lipids troubles
   - Women who are pregnant or nursing
   - Uncontrolled cardiac troubles
   - Febrile patients (temperature > 37.5°C)
   - Patients with hernias on treatment areas
   - Patients with recent scarring in treatment areas
   - Neuropathy disorder
   - Damaged skin
   - Cryoglobulinemia
   - History of cold hypersensitivity such as cold urticaria or Raynaud disease
   - Transaminases (ALAT, ASAT, Gamma-GT) > 1.5 x normal range.
5. Women of child-bearing potential not able to use high effective methods of birth control during the study.
6. Patients suffering of any uncontrolled medical condition considered as significant in the Investigator's opinion.
7. Vulnerable subjects according to the French Law : minors, pregnant women, adults under guardianship, individuals deprived from liberty, hospitalized subjects without consent and not protected by the Law, subjects admitted in a health or social institution for other aims than the research, major subjects unable to express their consent.

9.2.3 Exclusion criteria

- Subject consent withdrawal
- Decision of the Investigator or the Sponsor to withdraw the subject from the study.

9.3 TREATMENT PROCEDURE

9.3.1 Identification and description of the medical device under investigation

The Cryolipolysis Cristal is a class IIa medical device which consists to apply a controlled cooling on the fat deposits located on the body. Cooling is generated by an effect Peltier device.

The Cryolipolysis Cristal is dedicated to treat the located pocket of fat. It allows to improve the skin texture and significantly reduces the located fat layers. It is equipped with two handpieces allowing to treat simultaneously two areas.

This medical device is intended for doctor's offices; it has an EC marking following the 93/42/CEE directive.

The Cryolipolysis Cristal is manufactured by the Sponsor of the clinical investigation:

DELEO S.A.S

Technoparc EPSILON

300, rue Isaac Newton

83700 St Raphaël

Two Cryolipolysis Cristal were used in this study:

The complete identifications of the MDs were the following:

- Serial number: 2015155 and 2015100
- Software Version: System v2.1 20150924-3
- Type of the used handpieces: Ruby
- Serial number of the used handpieces: 141520926**,** 141640610, 141620717,141620716

The Cryolipolysis Cristal is composed of a thermo-lacquered aluminium structure, of a painted aluminium protective envelop, a touch-sensitive screen of control, a cooling generator, a non-invasive aspiration system of the skin, a water circuit and some control sensors. Two handpieces, allowing to aspire the fat deposits and cool it in a non-invasive manner, can simultaneously operate on two separate body zones.

Each handpiece is constituted by four Peltier effect modules allowing to decrease the temperature down to -8°C and equipped with a depressurisation system aiming to aspire the fat deposits in a non-invasive manner.

Handpieces are in indirect contact with the patient. Indeed, the skin is protected thanks to an alcohol and glycerine gel and to a protective wipe applied on the skin before positioning the handpiece.

9.3.2 Method of Assigning Subjects to Treatment Groups

No treatment groups in this study

9.3.3 Timing of treatment

The duration of the handpieces functioning on the skin was planned to be 60 minutes.

9.3.4 Blinding

This study was conducted through an open design.

9.3.5 Prior and Concomitant Therapy

Use of concomitant medication had to be recorded in the subject's medical file (drug name, dose, indication and dates of start and stop).

9.3.6 Treatment Compliance

Not applicable since no products were dispensed to the subjects. The treatment procedure was performed by the Investigator coordinator at the investigational site.

9.4 EFFICACY AND SAFETY VARIABLES

9.4.1 Efficacy and Safety Measurements

9.4.1.1 Demographics and Baseline Characteristics Assessed

9.4.1.1.1 Demographics

Demographic data: birthday date, initials, sex, size, weight, BMI, arterial pressure, heart beat, temperature, waist size, hip size, thigh circumference, chest size were recorded at the screening visit.

Weight, BMI, arterial pressure, heart beat, vital signs, temperature, ECG, urinalysis, blood sampling, waist size, hip size, thigh circumference, chest size were performed at every visit.

9.4.1.2 Efficacy Measurements

9.4.1.2.1 Caliper Measurements

Measure of the greasy fold thickness in millimeter using the caliper (John Bull harpenden skinfold calipers, England) at each visit.

9.4.1.2.2 Echography measurements

Measure of the subcutaneous fat thickness in centimeter by echography at V2 (before and after Cristal procedure), V3 and V4.

The instrument was a LOGIQ 9 (General Electric Medical Systems, USA) used with a 10MHz probe set at 8 cm of investigation depth.

On the echographic image, the subcutaneous fat thickness was considered as the area between the derrmis/hypodermis interface and the subcutaneous fascia. The subcutaneous fat thickness was measured by image analysis (dedicated software of the LOGIQ 9) along three lines: the central vertical line, and two equidistant vertical lines on the right and left sides as shown in example of the Figure 1 below:

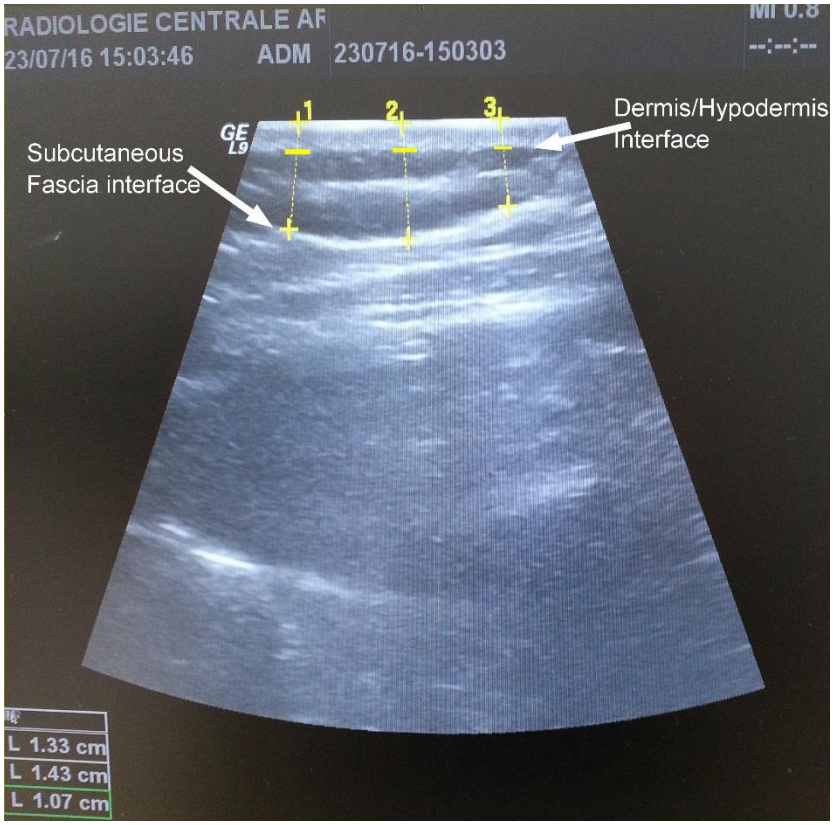
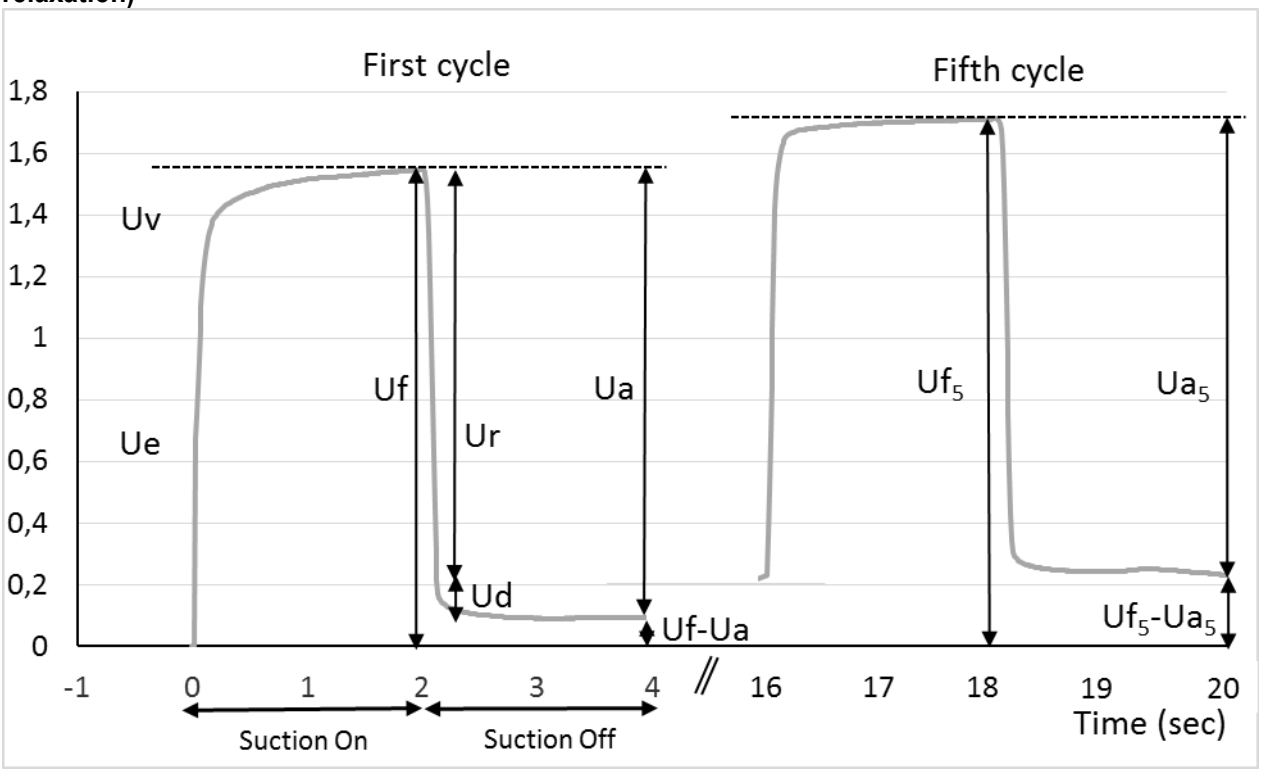


Figure 1: Example of subcutaneous fat thickness measurement between Dermis/hypodermis interface and the Subcutaneous fascia interface.

9.4.1.2.3 Elasticity measurements

The biomechanical properties of the skin were measured at V2, V3 and V4 using a Cutometer® DUAL probe (Kourage & Kazhaka, Germany). The Cutometer® uses a suction method (12) (13), to measure a deformation perpendicular to the skin surface. A negative pressure of 450 mbars is applied to the skin through the probe for 2 seconds, followed by a relaxation period of 2 seconds. This cycle is performed 5 times. The deformation induced on the skin is measured by an optical system located in the probe, whose aperture has either a 2 mm diameter for superficial measurements or 6 mm for deep measurements. The skin deformation curve as a function of time is described in Figure 2 below.

Figure 2: Skin deformation curve as a function of time (5 cycles of 2 sec deformation/2sec relaxation)



The Cutometer® DUAL probe is driven by a dedicated software which provide the following parameters after each set of measurement:

R0 = Uf, is the final distension of the first curve (total extensibility of the skin);

R1= Uf–Ua, is the ability to return to the original state;

R2= Ua/Uf, is the overall elasticity of the skin, including creep and creep recovery;

R3= Uf_5, is the last maximum highest point of the last curve;

R4= Uf_5-Ua_5, is the last minimal lowest point of the last curve;

R5= Ur/Ue, is the net elasticity;

R6= Uv/Ue, is the ratio of viscoelastic to elastic extension, also called the viscoelastic ratio;

R7= Ur/Uf, is the ratio of elastic recovery to the total deformation;

R8= Ua, is the recovery after of the first deformation;

R9= R3–R0, is the residual deformation at the end of the measuring cycle;

9.4.1.2.4 Photography

Standardized photographs were taken at each visit using a digital NIKON D90 camera equipped with a 60mm Nikkor lens f1/2.8 and flash Nikon speedlight sb-600. The settings of the camera, the lightening and the distance were standardized to provide reliable comparison of images between two different visits.

9.4.1.2.5 Medisol LED light lamp:

A LED lamp (Medisol, DELEO, 800 LED High power, 1 Watt/ LED, treatment area 52x30cm, electrical power 650W) was used just after the treatment procedure on one of the two target zones to reduce the edema after treatment procedure.

9.4.1.3 Safety Measurements

9.4.1.3.1 Clinical scores

Thirty minutes after treatment procedure, the Investigator had to assess reactions using clinical scores of erythema and oedema according to the following 4-point grading scale:

0:	Absent
0.5:	Doubtful
1:	Weak but well-defined
2:	Moderate
3:	Severe

9.4.1.3.2 Blood sampling

Glycaemia and lipids and hormonal status were assessed at each visit.

9.4.1.3.3 Evaluation of tolerance by the subject (pain, burning, fatigue)

The subject had to assess reactions of pain, burning, fatigue and others at the post-procedure visits.

9.4.1.4 AEs recording

The definition of AEs and SAEs as well as the means of reporting events and the rating of these are described in the protocol.

9.4.2 Primary Endpoint

- The primary endpoint was the thickness of greasy folds using the caliper at each visit

9.4.3 Secondary Endpoints

The secondary endpoints were the followings:

- the subcutaneous fat thickness by echography at V2, V3 and V4
- The skin elasticity using the Cutometer (at V2, V3 and V4)
- Sstandardized photographs of the target area at V2, V3 and V4
- Glycaemia and lipids status at each visit.
- Patient satisfaction at V3 and V4

9.5 DATA QUALITY ASSURANCE

9.5.1 Clinical Monitoring

DELEO SAS was responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the CRF. DELEO SAS could therefore assign a Clinical Research Associate (CRA) to monitor this study. The CRA's duties were to serve as the principle link between (co)Investigator(s) and DELEO SAS and advise the Investigator in the collection and maintenance of complete, legible, well organized, and easily retrievable data for the trial.

9.5.2 Data Management

The data management activities were performed by an independent consultant (LD). Computerized edit checks and review processes were performed on an ongoing basis until all data clarifications were resolved. The data were exported to be stored in appropriate format. After all data clarifications had been resolved and subject's evaluability determined, the database was locked.

9.5.3 Audit

The Sponsor was responsible for making sure that both its representatives (Monitor, CRA, etc.) and the Investigator fulfilled the requirements as specified by the GCP Guidance.

Audits of the study center could be conducted by the Sponsor/Clinical Research Organization (CRO) representatives.

9.6 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.6.1 Statistical and Analytical Plans

9.6.1.1 Variables to be analyzed

- Demographic variables were described for all patients included in the analyses.
- Greasy fold thickness using the caliper
- Subcutaneous fat thickness using echography
- Measure of skin elasticity using the Cutometer (Biomechanics parameters)
- Glycaemia and lipids status

9.6.1.2 Data Transformations

No data transformations were planned for this study

9.6.1.3 Populations Analyzed, Evaluability and Limitation/Evaluation of Bias

All randomized subjects who received the treatment and who contributed to any efficacy data to the study comprised the full analysis set (FAS) and were analysed for efficacy.

A per protocol (PP) analysis set was defined by the exclusion from the FAS of any subjects who did not fulfil all of the inclusion criteria or who met any of the exclusion criteria.

All subjects who received the treatment and for whom the presence or confirmed absence of AEs was available were included in the safety analysis set and analysed for safety.

9.6.1.4 Data Presentation and Graphics

Demographics, other baseline characteristics, local tolerance and AEs are presented using descriptive statistics (data summaries, listings, and figures).

Summary tables of primary and secondary endpoints are presented by treatment and for each part of the test zone using descriptive statistics (mean, SD, median, min, max and N).

9.6.1.5 Statistical Analysis

The qualitative variables were described descriptively in Tables with number of subjects and percent. The continuous variables were presented in Table (mean, standard deviation, minimum and maximum)

Before any statistical analysis, le normality of variables was checked using a Shapiro-Wilk test. Comparisons were intra-individual.

For the principal criterion, the greasy fold thickness after 2 months of treatment, the comparison Day56 versus Baseline was performed using a Student t test for paired data.

The objective to obtain a reduction of at least 30% of the greasy fold thickness was checked by the calculation of the 95% interval of confidence of the mean reduction of the thickness at T2month. The reduction of 30% had to be comprised within this interval of confidence.

Secondary criteria:

The comparison Day56 versus Baseline was performed using a Student t test for paired data for normal distributed variables and using a Wilcoxon signed rank test non normal variables.

9.6.1.6 Software and Dictionaries

Statistical software SYSTAT version 11.0 (SPSS, USA). MedDRA (Medical Dictionary for Regulatory Activities) version 19.0 was used for coding of adverse events.

9.6.2 Determination of Sample Size

A total of 20 subjects completing the study was needed to allow the detection of a significant reduction of 2 cm of greasy fold thickness (caliper) between Day56 and Baseline with 95 % probability and an alpha risk of 0.05 and estimating a common standard deviation of 2.1 cm.

9.7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

9.7.1 Protocol Amendments

No amendments were done.

9.7.2 Changes to Planned Statistical Analysis

No changes were made to the planned statistical analysis.

9.7.3 Other Changes to Planned Study Conduct

There were no other changes to the planned study conduct.

10 STUDY SUBJECTS

Results are presented and discussed on the basis of the study database and on the statistical report.

10.1 DISPOSITION OF SUBJECTS

One center (Dermatology department, Hôpital l'Archet 2, 0620 Nice, France) screened 20 subjects who were included in the study as planned.

10.2 PROTOCOL DEVIATIONS

No major protocol deviations were identified in this study.

10.3 STUDY ANALYSIS SETS

10.3.1 Full Analysis Set

The FAS was defined as all subjects who received the study treatment and who contributed to efficacy data. The FAS comprised all 20 included subjects Thus, FAS consists of 20 subjects.

10.3.2 Safety Analysis Set

The safety analysis set was identical to the FAS set and consists of 20 subjects.

10.3.3 Per Protocol Analysis Set

All randomized subjects who fulfilled all of the inclusion criteria and who did not meet any of the exclusion criteria. The Per Protocol (PP) analysis set consists of 20 subjects.

As PP and FAS are similar, all efficacy tables are performed on FAS only.

10.4 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

10.4.1 Demographic and Medical Baseline Characteristics

Demographic anatomical data are detailed in Table 2 and

No statistically significant evolution of weight and BMI were observed during the study compared to baseline values (See Statistical Appendix, § 3.2).

Table 3 below. At Screening the mean age was 45 years (from 28 to 65 years). Most of subjects were females (75%).

Table 2: Demographic Data at Screening visit

Demographic data		All randomized (N=20)	Females (N=15)	Males (N=5)
Age (years)	**mean**	**45**	**43**	**54**
	SD	13	11	15
	min	28	28	28
	max	65	63	65
Height (cm)	**mean**	**165**	**161**	**179**
	SD	11	9	5
	min	146	146	173
	max	187	175	187
Weight (kg)	**mean**	**90**	**84**	**119**
	SD	15	12	20
	min	65	65	100
	max	120	105	120
BMI	**mean**	**33**	**32**	**34**
	SD	2	2	1
	min	30	30	32
	max	35	35	35

No statistically significant evolution of weight and BMI were observed during the study compared to baseline values (See Statistical Appendix, § 3.2).

Table 3: Anatomical parameters at the Screening Visit

ANATOMICAL DATA		Waist size (cm)	Hip size (cm)	Thigh circumference (cm)	Chest size (cm)
Females	**mean**	**102**	**114**	**64**	**108**
	SD	12	9	6	7
	min	85	96	55	96
	max	120	126	74	124
Males	**mean**	**129**	**124**	**67**	**124**
	SD	16	16	9	12
	min	110	113	61	111
	max	150	150	82	138

No statistically significant variations of the anatomical parameters were observed during the study (See Statistical Appendix, § 3.2).

Specific criteria for women:

Among the 15 females, 12 were of childbearing potential and were using an effective contraception method during the study.

Concomitant therapies:

Overall, 9 (45%) subjects reported at least one concomitant therapy. The most frequently reported concomitant treatments were contraceptives, treatment of diabetes (n=2) and hyperthyroid (n=2). None of these therapies were judged to interfere with the evaluations in this study. Detailed information on concomitant therapies is provided in the database.

Vital signs, electrocardiogram and physical examinations:

At screening, vital signs were normal for all subjects. Some significant but not clinically relevant variations were observed during the study for the diastolic pressure, heartbeat and temperature. Some abnormalities were found on the electrocardiogram examination of 7 subjects but were judged as non-clinically significant.

10.5 MEASUREMENT OF TREATMENT COMPLIANCE

Since the treatment procedure was performed a trained Investigator, compliance to treatment was ensured.

11 EFFICACY EVALUATIONS

11.1 PRIMARY ENDPOINT

11.1.1 Greasy fold thickness measured by Caliper

The primary endpoint was to reduce from at least 30% the greasy fold thickness after 2 months of the Cristal Cryolipolysis treatment using the caliper tool measurement. Greasy fold thickness mean values at each visit and change from screening visit in percentage are shown in Table 4 below. Results of statistical comparisons are displayed in Table 5 (Statistical Appendix, § 4).

Table 4: Greasy fold thickness mean values (cm) at each visit and change from Screening visit in percentage (Caliper)

		Screening	Day 0	T1month	T2month	T1month vs Screening (%)	T2month vs Screening (%)
Zone 1 Without LED	m	4.9	4.9	3.9	3.6	-19.8%	-27.1% *
	sd	1.1	1.1	1.0	1.0	12.3%	13.7%
Zone 2 With LED	m	4.9	4.9	3.9	3.5	-21.4%	-29.1% *
	sd	1.0	1.0	1.1	0.9	11.3%	12.3%

*: reduction of -30% within the interval of confidence IC95%

IC95% for Z1 = [-20.1, -33.5]; IC95% for Z2 = [-23.2, -35.1]

Table 5: Greasy fold thickness using caliper, statistical comparisons versus Screening Visit

		Day 0 vs Screening	T1month vs Screening	T2month vs Screening	T2month vs T1month
Zone 1 Without LED	p value	ns*	<0.001	<0.001	0.001
Zone 2 With LED	p value	ns**	<0.001	<0.001	0.002

*ns: difference statistically non-significant (p>0.05)

Table 4 and Table 5 indicate that, following the Cristal Cryolipolysis treatment, the greasy fold thickness decreased whatever the post-treatment with LED or not. Compared to the Screening visit, the greasy fold

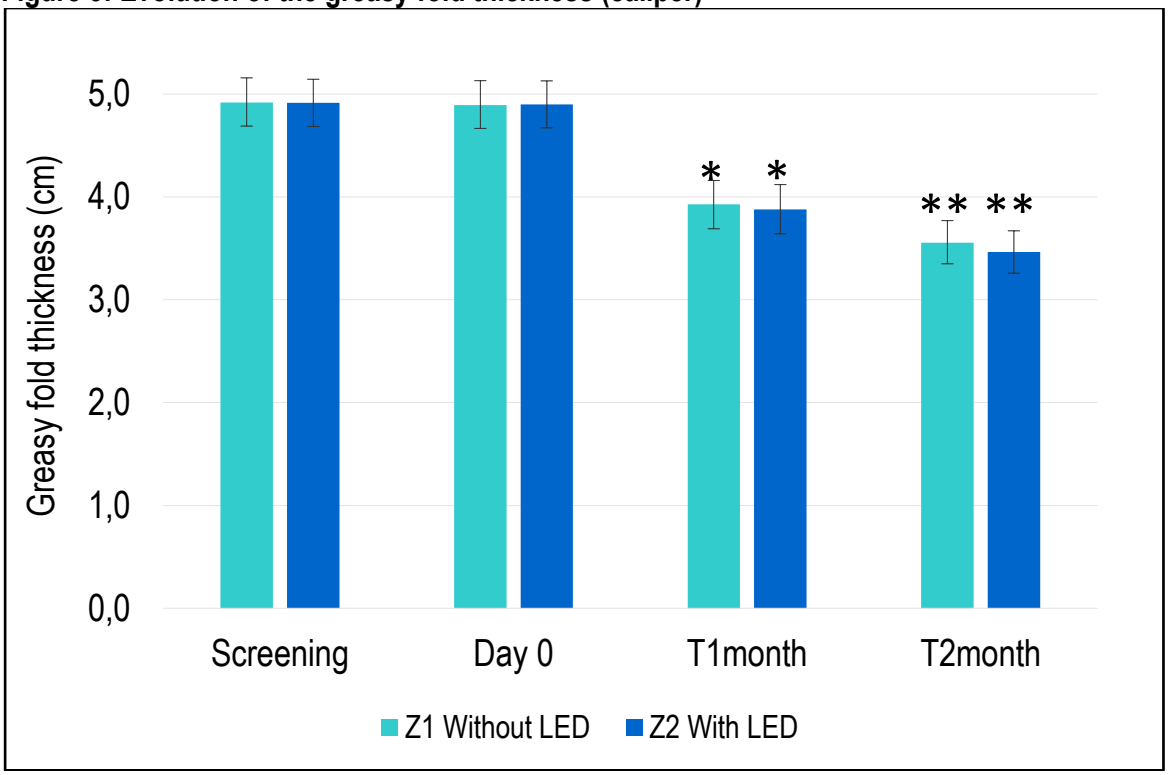
thickness was significantly reduced at T1month and T2month. This reduction was significantly lower at T2month compared to T1month.

The primary endpoint was reached at T2month because the percentage of reduction from at least 30% was comprised within the 95% interval of confidence of the mean percentage of thickness reduction.

Indeed, the reduction of 30% was comprised within the range IC95% [-20.1%, -33.5%] for the zone without LED post-treatment and within [-23.2%, -35.1%] for the zone with LED post-treatment. This was confirmed by the comparison of both percentages to the -30% reference value (see Statistical Appendix).

The evolution of the greasy fold thickness measured using caliper is shown on Figure 3 below.

Figure 3: Evolution of the greasy fold thickness (caliper)



*: *significantly different from screening and Day 0 (p<0,001)*

**: *significantly different from screening, Day 0 (p<0,001) and T1month (p<0,006)*

11.1.2 Greasy fold thickness, Zone 1 and Zone 2 averaged

In order to have a global value by subject, the greasy fold thickness measures obtained on the Zone 1 and Zone 2 were averaged.

The results indicate (see Statistical Appendix, §5.2) that the greasy fold thickness was reduced in average by -21% at T1month and -28% at T2month. The reduction of -30% was found inside the interval of confidence of the value at T2month [-22.1%, -34.1%].

11.1.3 Comparison of Zone 1 and Zone 2 (LED effect)

In order to evaluate the effect of LED exposure on the greasy fold thickness measured by caliper a comparison of Zones 1 and 2 was performed using an analysis of variance (ANOVA). No significant LED effect on the greasy fold thickness was detected whatever the evaluation visit.

11.2 SECONDARY ENDPOINTS

11.2.1 Subcutaneous fat measured by echography

Echography subcutaneous fat thickness mean values at each visit and change from Before procedure in percentage are shown in Table 6 below. Results of statistical comparisons are displayed in Table 7 (Statistical Appendix, § 5.1).

Table 6: Echography subcutaneous fat thickness mean values (cm) at each visit and change from Screening visit in percentage (echography)

		Before	After	T1month	T2month	After vs Before	T1month vs Before	T2month vs Before
Zone 1 Without LED	m	1.96	1.93	1.57	1.53	-3.55%	-19.65%	-23.37%
	sd	0.62	0.70	0.52	0.58	13.11%	13.61%	14.00%
Zone 2 With LED	m	1.91	2.06	1.56	1.44	7.97%	-18.99%	-24.17%
	sd	0.66	0.77	0.62	0.56	18.48%	14.19%	14.91%

Table 7: Echography subcutaneous fat thickness, statistical comparisons versus Before Treatment

		After vs Before	**T1month vs Before**	**T2month vs Before**	**T2month vs T1month**
Zone 1 Without LED	p value	ns*	<0.001	<0.001	ns*
Zone 2 With LED	p value	ns*	<0.001	<0.001	ns*

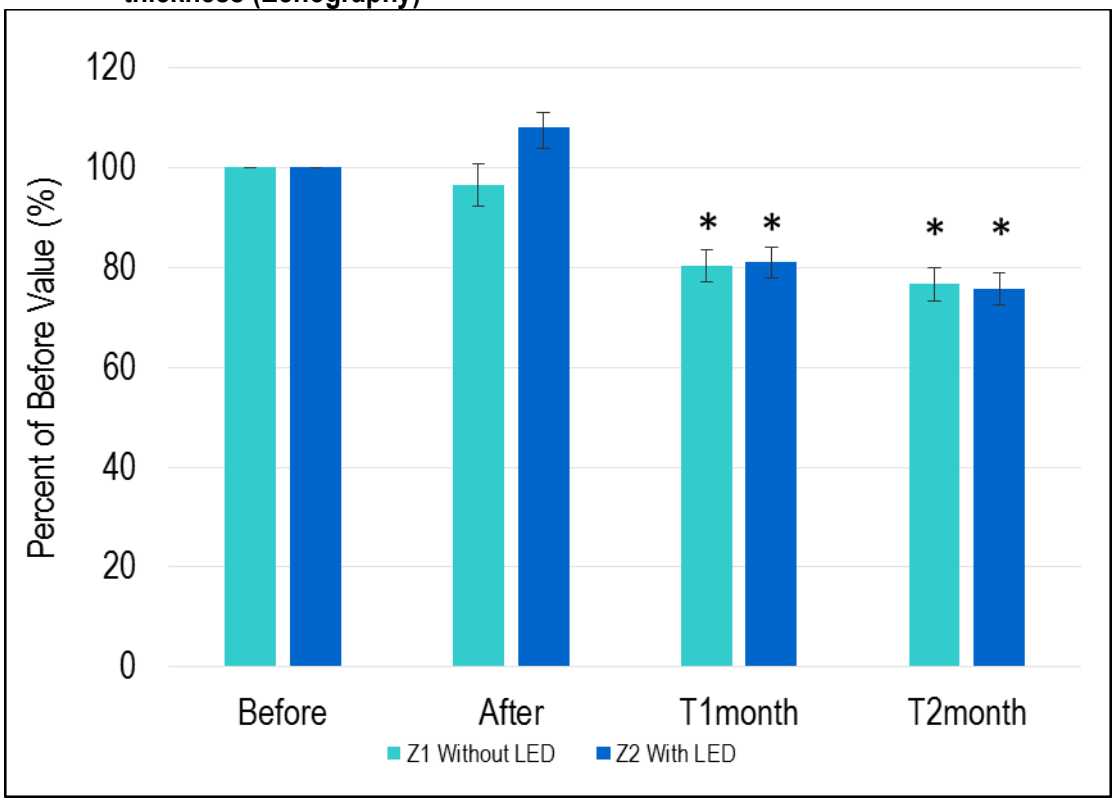
*ns: difference statistically non-significant (p>0.05)

Tables 6 and 7 indicate that, following the Cristal Cryolipolysis treatment, the subcutaneous fat thickness, measured by echography, decreased whatever the post-treatment with LED or not. Compared to the Before treatment value, the subcutaneous fat thickness was significantly reduced at T1month and

T2month. There was no significant difference between Before and After values. The mean thickness value seemed to decrease between T1month and T2month but the difference was not significant. At T2month, the reduction of fat thickness measured by echography was about -24%.

The evolution of the subcutaneous fat thickness measured by echography is shown on Figure 4 below.

Figure 4: Evolution in percentage from the Before procedure value of the subcutaneous fat thickness (Echography)

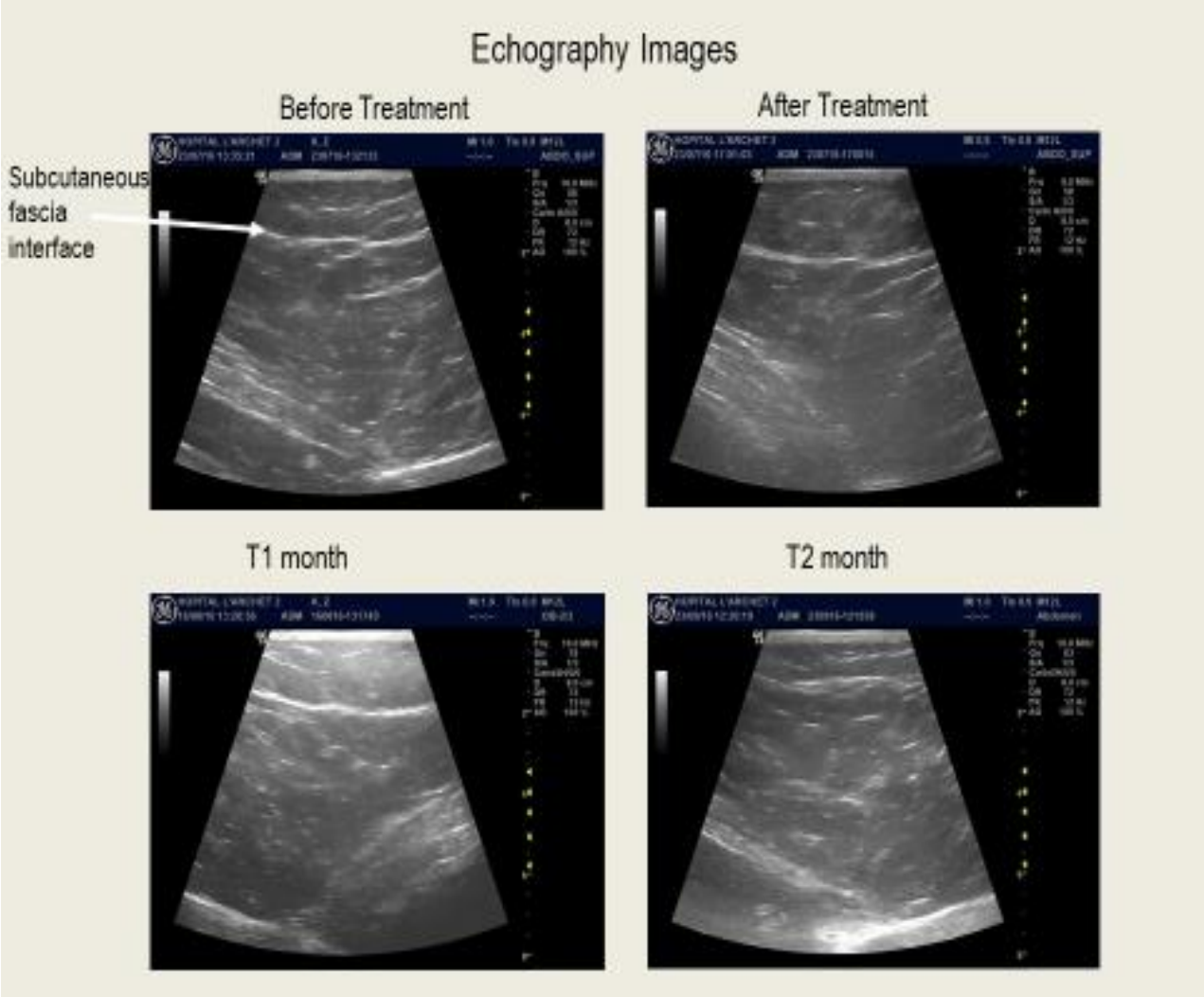


*: *significantly different from Before Cristal procedure (p<0,001)*

Typical echography images obtained before and after treatment are illustrated by the

Figure 5 below for one subject.

Figure 5: Typical echography images (before and after procedure)



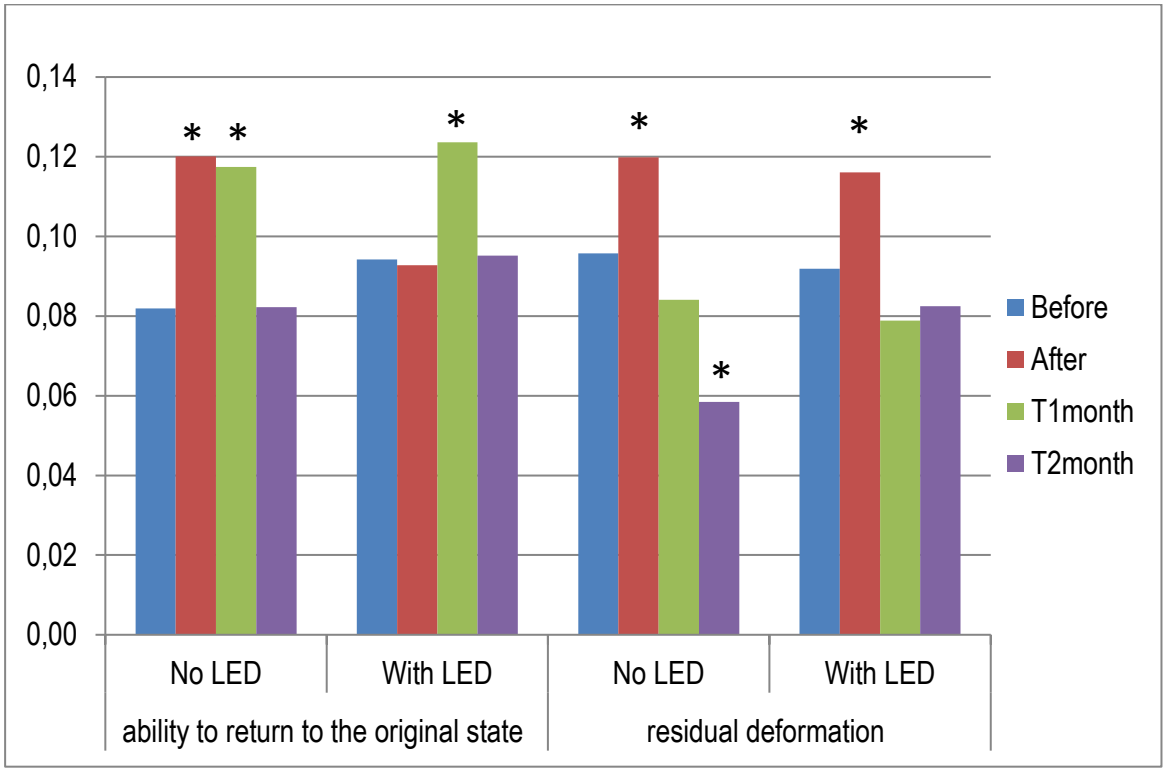
11.2.2 Measure of skin elasticity using the Cutometer

The details of descriptive statistics and statistical analyses concerning the biomechanical parameters are located in the Statistical report (Appendix 16.1.9). Only results related to skin elasticity and skin firmness are presented graphically in the Figure 6 and Figure 7 below.

The ability to return to the initial state (after one deformation) is presented in Figure 6. At T2month, the ability to return to the initial state is equal to its value Before treatment whatever the post-treatment. The residual deformation after 5 cycles is also maintained at T2month compared to Before treatment and it is even lower on the zone not LED post-treated. Both parameters are related to skin firmness.

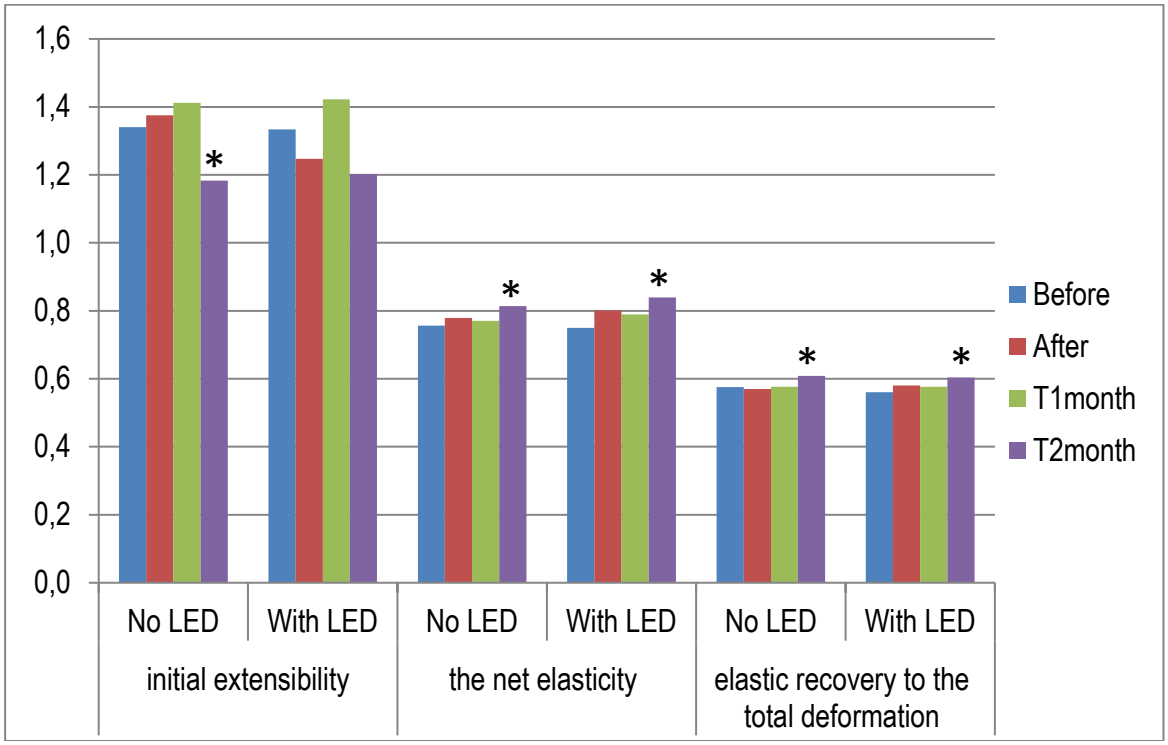
In Figure 7, the initial extensibility is not changed at T2month on the LED post-treated zone and is decreased a little on the not post-treated zone. It is interesting to note that the net elasticity and the elastic recovery after the total deformation are significantly increased two month after treatment procedure on both types of zones (LED post-treated or not).

Figure 6: Skin biomechanics related to firmness



*: *significantly different from Before treatment procedure (p<0,001)*

Figure 7: Skin biomechanics related to elasticity

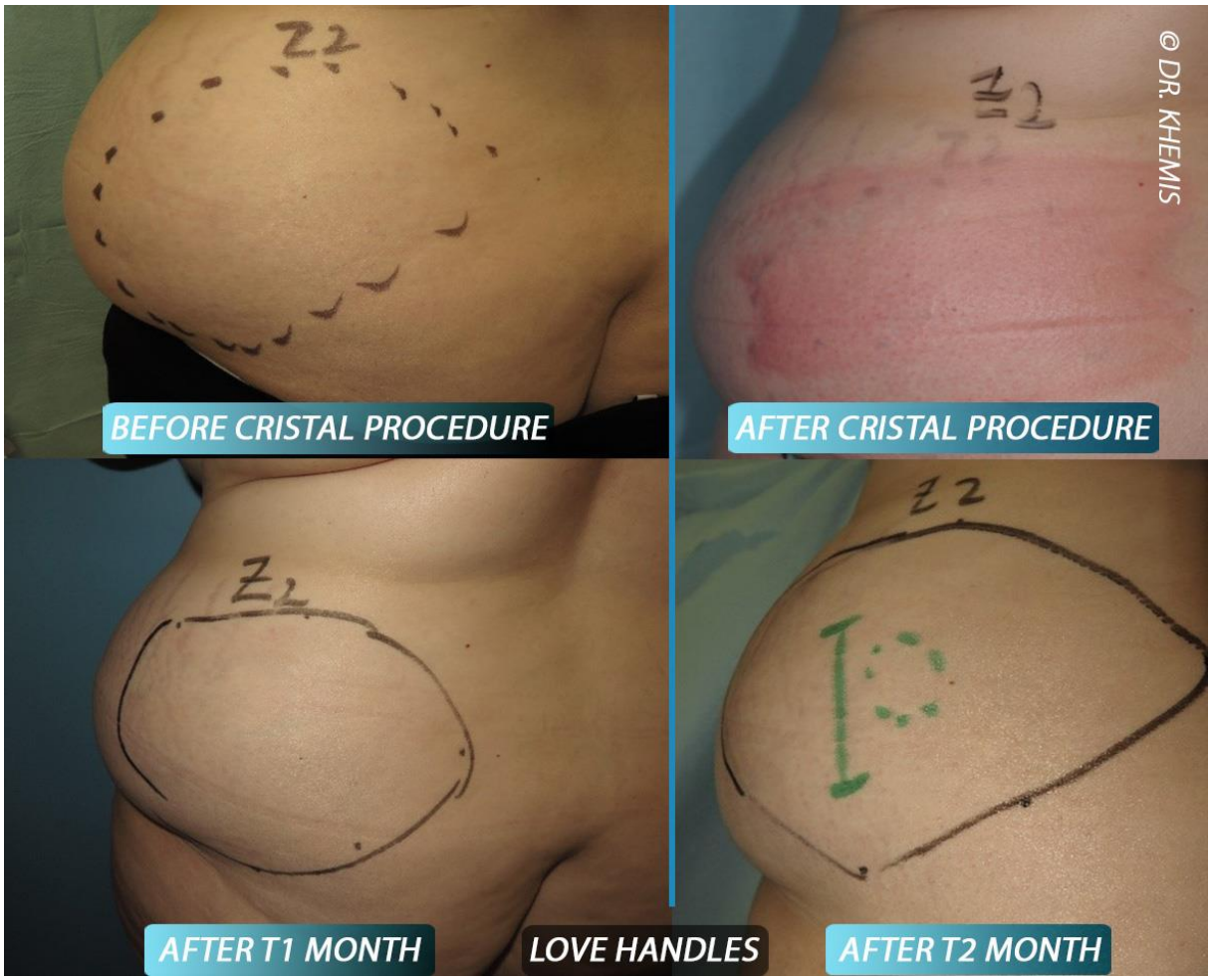


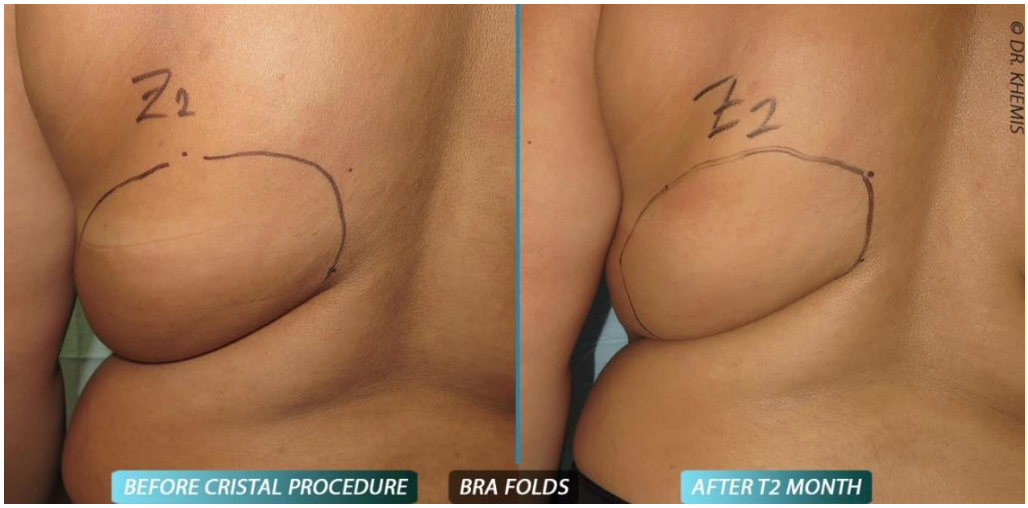
*: *significantly different from Before treatment procedure (p<0,001)*

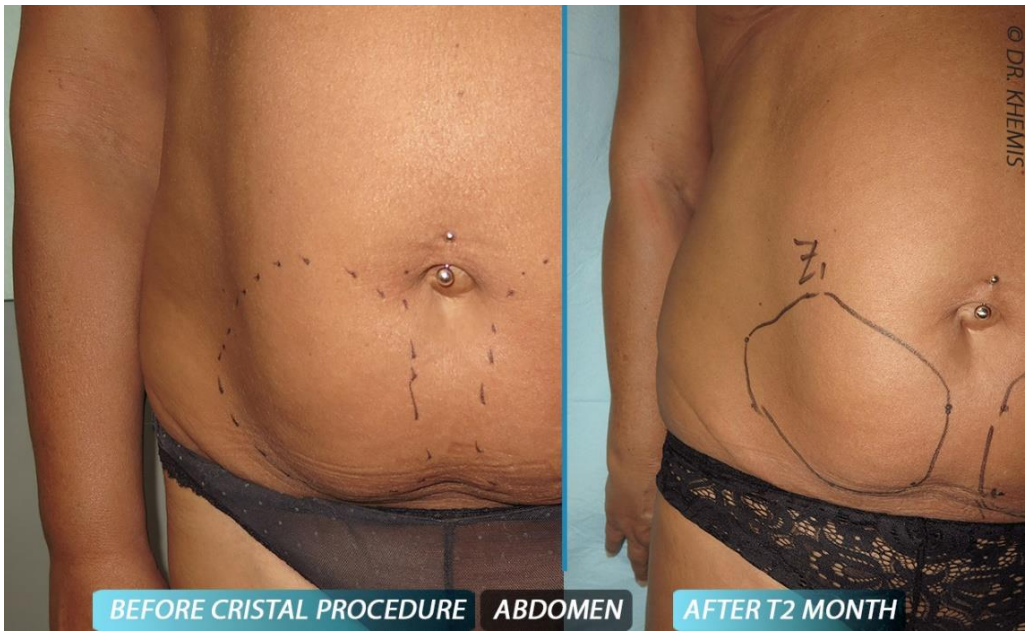
11.2.3 Standardized photographs

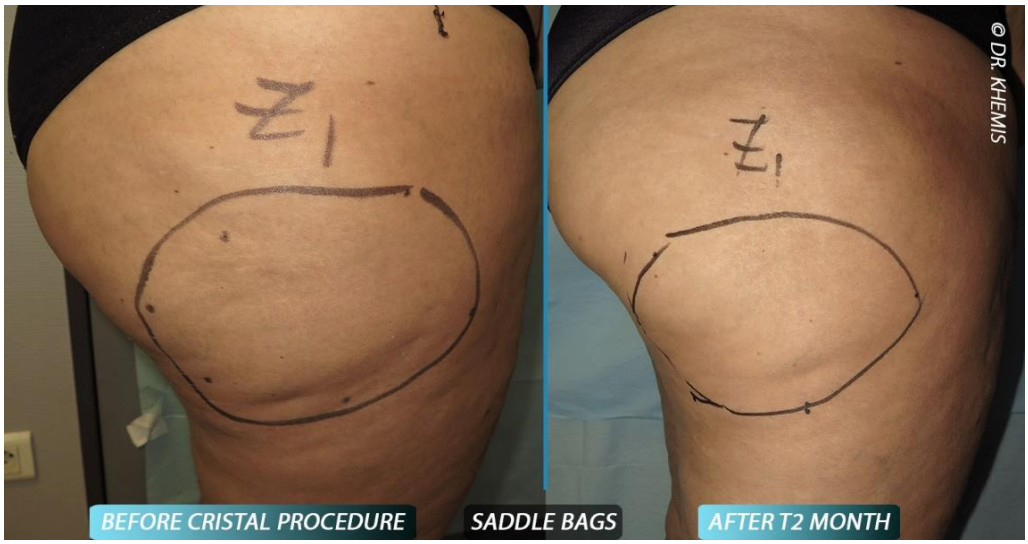
Standardized photographs of target zones were taken at each visit. This documentation was stored in a CD disk for further uses. Examples of photographs are shown in Figure 8 below:

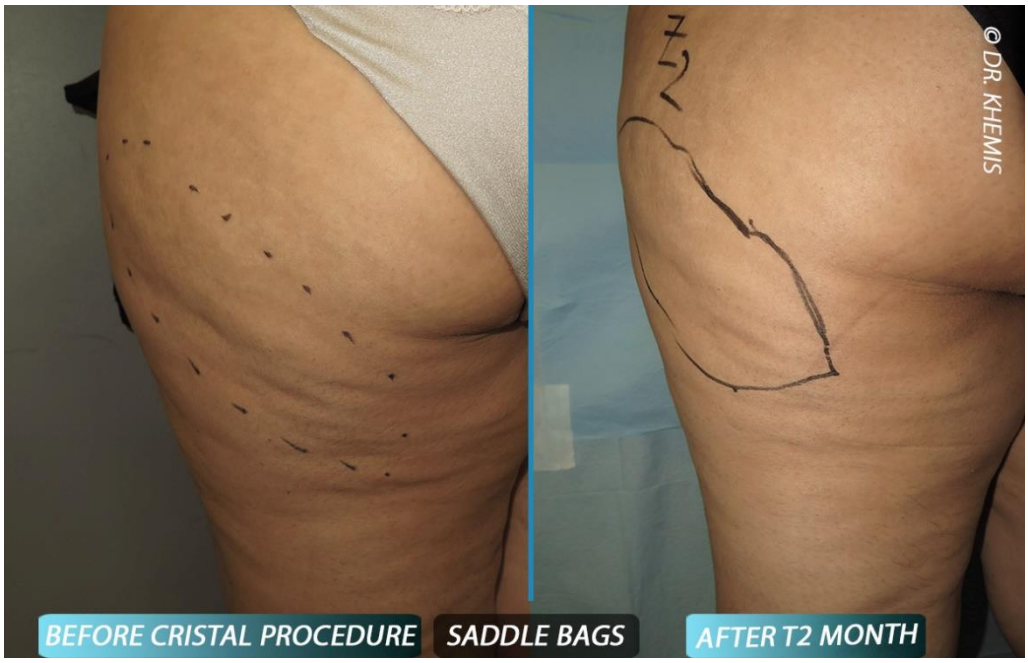
Figure 8: Standardized photographs of the target areas

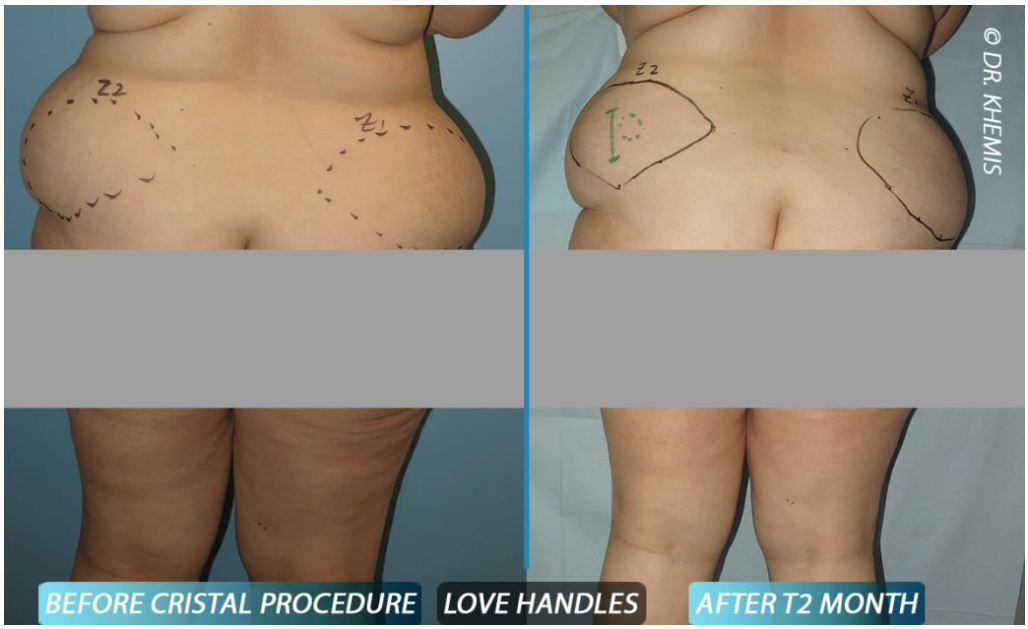

BEFORE CRISTAL PROCEDURE
AFTER CRISTAL PROCEDURE
© DR. KHEMIS
AFTER T1 MONTH
LOVE HANDLES
AFTER T2 MONTH


BEFORE CRISTAL PROCEDURE
BRA FOLDS
AFTER T2 MONTH
© DR. KHEMIS


© DR. KHEMIS
BEFORE CRISTAL PROCEDURE
ABDOMEN
AFTER T2 MONTH


© DR. KHEMIS
BEFORE CRISTAL PROCEDURE
SADDLE BAGS
AFTER T2 MONTH


© DR. KHEMIS
BEFORE CRISTAL PROCEDURE
SADDLE BAGS
AFTER T2 MONTH


© DR. KHEMIS
BEFORE CRISTAL PROCEDURE
LOVE HANDLES
AFTER T2 MONTH

11.3 EFFICACY CONCLUSION

Results of the primary criterion indicated the greasy fold thickness decreased whatever the post-treatment with LED or not. Compared to the Screening visit, the greasy fold thickness was significantly reduced at T1month and T2month. This reduction was even significantly lower at T2month compared to T1month.

The primary endpoint was reached at T2month because the percentage of reduction from at least 30% was comprised within the 95% interval of confidence of the mean percentage of thickness reduction. No significant LED effect on the greasy fold thickness was detected whatever the evaluation visit.

Concerning the secondary endpoint, the fat deposits thickness, measured by echography, decreased whatever the post-treatment with LED or not. Compared to the Before treatment value, the fat deposits thickness was significantly reduced at T1month and T2month. There was no significant difference between Before and After treatment values. The mean thickness value seemed to decrease between T1month and T2month but the difference was not significant. At T2month, the reduction of fat thickness measured by echography was about -24%.

Concerning biomechanics properties of the skin, the results indicated that the Cristal Cryolipolysis procedure did not affect the skin firmness skin and even slightly improve the skin elasticity at T2month for both types of zones.

12 SAFETY EVALUATION

12.1 BLOOD ANALYSES

12.1.1 Glycaemia

Descriptive statistics of glycaemia are detailed in the Table 8 below:

Table 8: Descriptive statistics of Glycaemia during the study (mmol/l)

	Screening	Day 0	T1month	T2month	**Normal range**
N	20	18	20	20	3.5 – 5.8 mmol/l
Mean	**4.98**	**4.91**	**4.93**	**5.02**	
Standard Dev	0.867	0.555	0.889	1.259	
Minimum	4.04	4.01	3.96	3.83	
Maximum	7.91	5.92	7.72	9.82	

Normal range: 3.90 – 5.80 mmol/l

No change of glycaemia were observed during the study. Some patients had hyperglycaemia values due to their obesity state.

12.1.2 Lipids status

Descriptive statistics of lipids status are detailed in Table 9 and Table 10 below with results of statistical comparisons:

Table 9: Descriptive statistics of Cholesterol total and Triglycerides

Cholesterol Total (g/l)	Screening	Day 0	T1month	T2month	Normal range
N	20	20	20	20	1.35 – 2.00 (g/l)
Mean	**2.17**	**2.12**	**2.06**[Scr, T2]	**2.15**	
Standard Dev	0.40	0.39	0.38	0.33	
Minimum	1.43	1.22	1.26	1.51	
Maximum	3.05	2.98	2.95	2.60	
Triglycerides (g/l)	**Screening**	**Day 0**	**T1month**	**T2month**	0.45 – 1.50 (g/l)
N	20	20	20	20	
Mean	**1.36**	**1.34**	**1.40**	**1.56**	
Standard Dev	0.56	0.61	0.55	0.82	
Minimum	0.58	0.54	0.61	0.54	
Maximum	2.55	2.67	2.44	3.65	

Scr, T2: significantly different from Screening and T2month

Mean values of cholesterol total are higher than the normal range due to the obesity state of the subjects. There was a significant decrease of cholesterol total at T1month compared to Screening and T2month. No increase of cholesterol total was observed during the study. No significant increase of triglycerides was observed during the study.

Table 10: Descriptive statistics of Cholesterol HDL and LDL (g/l)

Cholesterol HDL (g/l)	Screening	Day 0	T1month	T2month	Normal range
N	20	20	20	20	> 0.40
Mean	**0.51**	**0.51**	**0.48**[Day0]	**0.50**	
Standard Dev	0.12	0.10	0.11	0.12	
Minimum	0.31	0.37	0.36	0.34	
Maximum	0.75	0.78	0.76	0.68	
Cholesterol LDL (g/l)	**Screening**	**Day 0**	**T1month**	**T2month**	< 1.60
N	20	20	20	19	
Mean	**1.39**	**1.34**	**1.30**[Scr]	**1.33**	
Standard Dev	0.37	0.34	0.32	0.30	
Minimum	0.82	0.65	0.70	0.67	
Maximum	2.24	2.16	2.00	1.79	

Scr, Day0: significantly different from Screening or Day0

Mean values of cholesterol HDL and LDL were located within the normal range. The mean values of HDL and LDL were stable during the study with a small decrease at T1month versus Day0 for HDL and versus Screening for LDL.

12.1.3 Hormonal status

Descriptive statistics of TSH (thyreostimulin) are detailed in Table 11 below.

Table 11: Descriptive statistics of TSH (Thyreostimulin)

TSH (thyreostimulin) (mUI/l)	Screening	Day 0	T1month	T2month	Normal range
N	20	20	20	20	0.55- - 4.78
Mean	**1.48**	**1.64**	**1.62**	**1.62**	
Standard Dev	0.55	0.76	0.66	0.84	
Minimum	0.66	0.11	0.111	0.11	
Maximum	2.52	2.87	3.09	3.56	

No significant variation of TSH was observed during the study.

Descriptive statistics of Free T4 (Free thyroxine) and Free T3 (Free triiodothyronine) are detailed in Table 12 below with results of statistical comparisons:

Table 12: Descriptive statistics of Free T4 and Free T3

Free T4 (pmol/l)	Screening	Day 0	T1month	T2month	Normal range
N	20	20	20	20	11.50 – 22.70
Mean	**15.76**	**14.24^{Scr}**	**13.77^{Scr}**	**14.77^{T1}**	
Standard Dev	2.40	1.51	1.63	1.72	
Minimum	12.20	11.80	10.90	12.00	
Maximum	20.90	19.00	17.90	17.50	
Free T3 (pmol/l)	**Screening**	**Day 0**	**T1month**	**T2month**	3.50 – 6.50
N	20	20	20	20	
Mean	**4.98**	**4.94**	**5.25^{Scr}**	**5.04^{T1}**	
Standard Dev	0.45	0.90	0.45	0.54	
Minimum	4.11	1.68	4.55	4.36	
Maximum	5.98	6.27	6.28	6.66	

Scr, T1: statistically different from Screening, T1month

Compared to Screening visit, at T1month, a significant decrease (-13%) was observed for Free T4 and a significant increase (+5%) of Free T3. These changes were not observed when compared to the Day0 levels just prior to Cryolipolysis procedure.

12.2 LOCAL REACTIONS OBSERVED JUST AFTER TREATMENT PROCEDURE

Local reactions observed just after treatment procedure with and without LED post-treatment are summarized in Table 13 below with results of statistical comparisons:

Table 13: Local reactions after treatment procedure

	Erythema		Oedema	
	With_LED	**Without_LED**	**With_LED**	**Without_LED**
N	19	19	19	19
Mean	**0,7***	**1,1**	**0,2+**	**0,6**
Standard Dev	0,6	0,8	0,4	0,8
Minimum	0,0	0,0	0,0	0,0
Maximum	2,0	2,0	1,0	2,0

*: significantly different from without LED (p=0.035, Wilcoxon signed rank test)

+: significantly different from without LED (p=0.033, Wilcoxon signed rank test)

The number of reactions observed by erythema and oedema scores are illustrated by the Figure 9 below:

Figure 9: Local reactions, number of erythema and edema scores

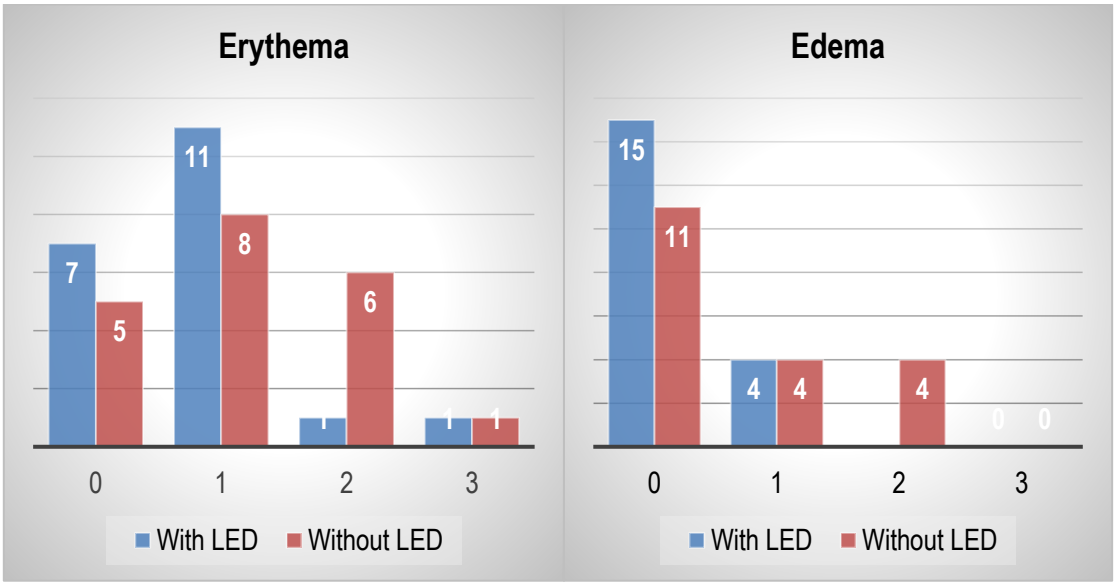


Figure 6 indicates that high scores of erythema and oedema were more numerous on the zone not post-treated by the LED whereas low scores were more numerous on the LED post-treated zone.

12.3 POST-PROCEDURE REACTIONS

The reactions observed during the post-procedure period and recorded at T1month are summarized in the Table 14 below:

Table 14: Post-procedure reactions

	Just on zone 1 (No LED)	Just on zone 2 (With LED)	On Both Zones
Pain	N=1	N=0	N=8 (7 moderate 1 severe)
Others	0	0	N=1 (Sensation of light anaesthesia)
Duration post-procedure	3 days	0	5 days in average for pain and 24h for anesthesia

This Table indicates that most of reactions were observed on both target zones with 8 pain sensations and 1 light anaesthesia. The mean duration of pain sensations was during the 5 days following procedure treatment. For one subject, a pain sensation was felt only on the target zone not exposed to the LED light (during 3 days).

12.4 ADVERSE EVENTS (AEs)

12.4.1 Brief Summary of AEs

A total of 2 (10%) subjects experienced a total of 2 AEs. One AE concerned a pregnancy revealed by the pregnancy test of the last visit. This AE was judged by the investigator as non-related to the study content. The second AE was a severe local urticaria-like reaction observed just after the Cristal procedure (cold urticaria, AE related to treatment). This AE was resolved within a few hours.

12.4.2 Display of AEs

All AEs were summarized by System Organ Class (SOC) and Preferred Terms (PT) based on the MedDRA dictionary in Table 15 below:

Table 15: AEs by Primary SCO and PT

Primary System Organ Class (SOC)	Preferred Term (PT)	Number of subjects	%
Skin and subcutaneous tissue disorders	Angioedema and urticaria	1	5%
Pregnancy, puerperium and perinatal conditions	Unintended pregnancy	1	5%
Total number of AEs		**2**	**10%**
Total number of subjects		**2**	**10%**

12.5 SAFETY CONCLUSIONS

Concerning blood examination, the glycaemia level was not affected by the treatment procedure. Mean cholesterol total values were found higher than the normal range due to the obesity state of the subjects. No increase of cholesterol total was observed during the study and even a significant weak decrease was observed at T1month compared to Screening and T2month. No significant variations of triglycerides was observed. The mean values of HDL and LDL were stable during the study with a small decrease at T1month versus Day0 for HDL and versus Screening for LDL.

Concerning the hormonal status, no significant variation of TSH was observed during the study. Compared to Screening visit, at T1month, a significant decrease (-13%) was observed for Free T4 and a significant increase (+5%) of Free T3. These changes were not observed when compared to the Day0 levels just prior to Cryolipolysis procedure. Thus, these variations can be judged as non-clinically relevant.

For post-procedure local reactions, a better tolerance was observed on LED treated zones with lower scores of erythema and edema. Fifty-five percent (55%) of subjects did not feel any painful post-procedure reactions and the mean duration of pain was 5 days for subjects experiencing pain.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 DISCUSSION

The primary objective of this trial was to reduce from at least 30% the greasy fold thickness after 2 months of the Cristal Cryolipolysis treatment using a caliper tool measurement.

The secondary objectives were:

- To assess the safety and tolerability of the Cristal Cryolipolysis treatment in the study
- To assess the satisfaction of patient with regards to efficacy and tolerability of the treatment.
- To assess the effects of LED light after Cristal Cryolipolysis treatment.

It was a single center, open study with intra-individual comparisons enrolling obese subjects (BMI: 30-35).

Twenty subjects were included and completed the study. Most subjects were females (75%). At Screening, the mean age of the subjects was 45 years (from 28 to 65 years).

The study was conducted as planned according to the protocol. No major protocol deviations were observed.

After only one treatment of Cristal Cryolipolysis, it was observed:

Results of the primary criterion indicated the greasy fold thickness decreased whatever the post-treatment with LED or not. Compared to the Screening visit, the greasy fold thickness was significantly reduced at T1month and T2month. This reduction was even significantly lower at T2month compared to T1month.

Therefore, the primary endpoint was reached at T2month because the percentage of reduction from at least 30% was comprised within the 95% interval of confidence of the mean percentage of thickness reduction.

Concerning the secondary endpoint, the fat deposits thickness, measured by echography, decreased whatever the post-treatment with LED or not. Compared to the Before treatment value, the fat deposits thickness was significantly reduced at T1month and T2month. There was no significant difference between Before and After treatment values. At T2month, the reduction of fat thickness measured by echography was about -24%.

Concerning biomechanical properties of the skin, the results indicated that the Cristal Cryolipolysis procedure did not affect the skin firmness and even slightly improve the skin elasticity at T2month for both types of zones.

Safety results showed that for the post-procedure local reactions, a better tolerance was observed on LED treated zones with lower scores of erythema and edema. Fifty-five percent (55%) of subjects did not feel any painful post-procedure reactions and the mean duration of pain was 5 days for subjects experiencing pain.

Concerning blood lipids, a decrease of blood cholesterol total, LDL and HDL was observed at T1month with normal level recovery at T2month. For the hormonal blood status, a decrease of Free T4 and an increase of Free T3 were measured at T1month with normal level recovery at T2month. No significant variations of TSH and no changes in glycaemia were measured during the study.

Two AEs were reported, one concerned a pregnancy revealed by the pregnancy test of the last visit. and judged by the investigator as non-related to the study content. The second AE was a severe local urticaria-like reaction observed just after the Cristal procedure (cold urticaria, AE related to treatment). This AE was resolved within a few hours.

There was no sign of aggravation in patients with stretch marks.

13.2 OVERALL CONCLUSIONS

In the conditions of this study, the Cristal Cryolipolysis treatment was found efficient and safe to treat the greasy folds in obese patients.

14 REFERENCES

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15 APPENDICES

15.1 STUDY INFORMATION

Appendix No.	Appendix Title	Status
16.1.1	Clinical Study Protocol and Amendments	
16.1.2	Sample CRF	
16.1.3	List of IEC or IRBs and Representative Written Information for the Subjects and Sample Consent Form	
16.1.4	List of Investigators and CV for International Coordinating Investigator	
16.1.5	Signatures of Principal or Coordinating Investigator(s)	
16.1.6	Listing of subjects receiving test drug(s)/Investigational product(s) from specific batches	NA
16.1.7	Randomization Scheme and Codes	NA
16.1.8	Audit Certificates	NA
16.1.9	**Statistical Appendix**	
16.1.10	Documentation of Inter-laboratory Standardization Methods	NA
16.1.11	Publications Based on the Study	NA
16.1.12	Important Publications Referenced in the Report	NA

15.2 SUBJECT DATA LISTINGS

Appendix No	Appendix Title	Status
16.2.1	Discontinued Subjects	NA
16.2.2	Protocol Deviations	NA
16.2.3	Subjects Excluded from the Efficacy Analysis	NA
16.2.4	DATA BASE	