CRYOSKIN 3.0

OBSERVATIONAL STUDY REPORT

Title: Study of the effectiveness of the Cryoskin 3.0 five-session protocol in slimming the abdomen on patients presenting an abdominal circumference less than 95cm (37.4 in.) in women and 102cm (40.1 in.) in men.

Protocol	**Cryoskin 3.0**
Director of study	Dr Phlippe Blanchemaison Vascular Medicine
Sponsor	PRODESIGN PLUS Mr Laurent Chevalier, President
Clinical Study Company	S.F.A.S , Societe Francaise d'Accreditation Sante 113, Av. Victor Hugo, 75116 Paris
Protocols Implementation	Stephanie Turco
Version / Date	3.9 / September 10, 2018

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SUMMARY OF THE STUDY

TITLE	**Cryoskin 3.0 Protocol : Study of the effectiveness of Cryoskin 3.0 five-session protocol in slimming the abdomen on patients presenting an abdominal circumference less than 95cm (37.4 in.) in women and 102cm (40.1 in.) in men**
OBJECTIVES	**Main objective:** The goal of the study is to evaluate the slimming effectiveness of Cryoskin 3.0 on the abdominal area, when following the treatment protocol conceived by Prodesign Plus. **Secondary objective:** Evaluate the safety of said protocol by monitoring side effects during the study.
METHODOLOGY	**Observational monocentric study based on 16 subjects, with criteria evaluation before and after the treatment.** **2 visits: Day 0 and Day 60** - **Day 0:** baseline visit (effectiveness criteria) - **Day 60:** final visit after 5 sessions with Cryoskin 3.0, to evaluate effectiveness and side effects.
STUDIED DEMOGRAPHIC Inclusion criteria	● Subjects 18+ and under 70 ● Waist circumference < 95cm for women and <102 cm for men ● Stable weight for 3 months before the start of the study
Exclusion criteria	● Subjects under 18 and over 70 ● Patients who started a weight loss program before the start of the study and who did not want to stop ● Pregnant and breastfeeding women ● Patients with chronic disease requiring an ongoing treatment
Number of subjects	Total : 16 subjects
Researchers - **Number** - **Country**	1 center France
PRODUCT UNDER STUDY Cryoskin 3.0	● Description: Cryoskin 3.0 is a cryotherapy device comprised of a control panel and a flat handpiece which can go up to 40 °C (104 °F) and go down to – 8 °C (17.6 °F) , in the context of the protocol ● Technique: cryotherapy, thermal shock ● Number of sessions: 5 ● Length of each session: 40 minutes ● Frequency: one session every 15 days
STATISTICS	The calculations done in Excel are: ● Minimum values ● Maximum values ● Average values

	● Variations in percentage ● Standard deviations ● Student's T-test
LENGTH OF STUDY (per subject)	**Maximum 3 months**
DATES (start/end)	First inclusion: March 2, 2018 Last visit: Week of June 25, 2018

STUDY SCHEDULE

	Screening	Inclusion	Cryoskin 3.0 Sessions					Last visit
Visit	**0**	**1**						**2**
Week	**Week 0**	**0**	**1 - 8**					**8**
Day	**Day 0**	**Day 0**						**Day 60**
Information – Consent	**X**	**X**						
Medical history		**X**						
Inclusion/exclusion criteria		**X**	**5 sessions of Cryoskin 3.0**					
Doppler Ultrasound 13 MHz (subcutaneous tissue thickness)		**X**						**X**
Impedance analysis (BMI, weight, % body fat)		**X**						**X**
Abdominal circumference (waistline)		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Digital pictures		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Effectiveness evaluation (satisfaction survey)								**X**
Data collection on adverse effects			**X**	**X**	**X**	**X**	**X**	
General tolerability of the treatment								**X**
Researcher	**Dr Blanchemaison**							

1 – Introduction

1.1 – Product : Cryoskin 3.0

1.1.1 – Description of the device

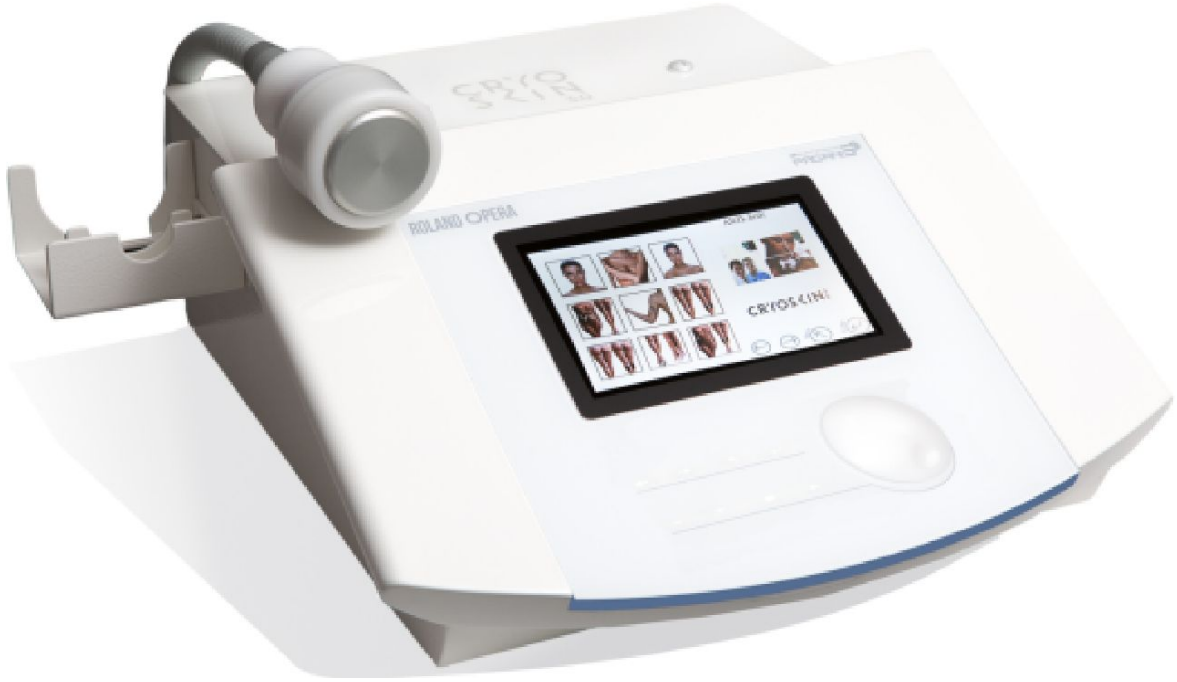
The device is comprised of:

- A digital control unit offering several treatment programs
- A mobile flat handpiece whose main function is based on the action of thermal shock, combining cryotherapy and thermotherapy.

The program studied here is dedicated to the slimming of the abdominal area.

The handpiece heats up the area at 40 °C for 2 minutes then cools (using the Peltier effect) down to -8 °C (17.6 °F) for 12 minutes then heats back up to 35 °C (95 °F).

A slow but constant motion associated with a specific manual manipulation prevents any risk of frostbite and allows the treatment of deep subcutaneous tissue.



The CryoSkin 3.0

Cryoskin 3.0 has obtained an EC certificate of conformity (see Appendix #1: "*Attestation CE Médicale*" - European Community Medical Certificate).

1.1.2 – Cryoskin 3.0's general indications

Cryoskin 3.0 is designed exclusively for the beauty industry. This device is commercialized in France, the European Union and the United States. **It is used for localized slimming and can treat the thighs (inner and outer), the entire belly, the abdominal circumference, the underarms, the back, the ankles, the face, and the chin.** It is also used to rejuvenate the face and firm the skin (on face and body).

1.2 – Thermal shock in fat cell destruction

1.2.1 – Cryotherapy and its slimming effect

Cryotherapy has been studied since 1944 for its multiple effects on inflammation, pain, blood flow/circulation, heart disease, etc. However, it has become the subject of great interest in the beauty and slimming industry since 2008, following Ross Anderson's study[1] on localized cryotherapy (selective cryolipolysis). Since then, it has been the focus of 61 studies about fat mass reduction, showing on average a 20% reduction. In 2008, Ross Anderson's study on pigs showed a 25% fat cell destruction on the treated area. More recent studies have proven the safety of the technique and its efficacy on 15% to 20% of the treated area. A scientific journal[2], published in 2008, which gathered 4 studies and 101 subjects, showed its effects on the overall appearance.

1.2.2 – Thermotherapy and its slimming effect

Thermotherapy combines the use of cool therapy and heat therapy. It consists of using an external heating source to influence the cellular metabolism. This thermal energy produces a biological response on the skin by activating mechanoreceptors sensitive to heat.
Thermotherapy takes many forms: sauna, application of heat, radiofrequency, laser.

When it comes to slimming, thermotherapy intervenes in two fundamental phenomena for the improvement of the *appearance.*
Thermotherapy increases the production of collagen by the fibroblasts (main skin cells) and helps to tone the skin. On *Pubmed*, the use of radiofrequency and its thermal effect on collagen production is the subject of 123 published studies between 1996 and 2018. A 2014 study[3] on 35 patients shows that applying a radiofrequency probe (at 42 °C, i.e. 107.6 °F) on a 3 cm^2 skin surface (0.46 in^2) for two minutes visibly improves skin firmness. According to a Visual Analogue Scale (VAS), the measured improvement represents 89%. In 2017, researchers performed a study which showed[4] that thermal action of radiofrequency helps fibroblasts' growth and consequently promotes collagenesis and angiogenesis.
At the fat cell level, several thermotherapy techniques can be used: laser, radiofrequency, etc. On *Pubmed*, radiofrequency has prompted 61 articles between 2003 and 2018. In 2010, an in vitro study[5] on adipocytes harvested from the abdomen shows that after being exposed to a temperature of 45 °C (113 °F) for 3 minutes only 60% of fat cells are still alive. The cell membrane breaks down, producing a lysis of the adipocytes (fat cell destruction).

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[1] Manstein D, Laubach H, Watanabe K, Farinelli W, Zurakowski D, Anderson RR. Selective cryolysis: a novel method of non-invasive fat removal. Lasers Surg Med. 2008 Nov;40(9):595-604.
[2] Lipner SR. Cryolipolysis for the treatment of submental fat: Review of the literature. J Cosmet Dermatol. 2018 Jan 17.
[3] Key DJ. Integration of thermal imaging with subsurface radiofrequency thermistor heating for the purpose of skin tightening and contour improvement: a retrospective review of clinical efficacy. J Drugs Dermatol. 2014 Dec;13(12):1485-9.
[4] Meyer PF, de Oliveira P, Silva FKBA, da Costa ACS, Pereira CRA, Casenave S, Valentim Silva RM, Araújo-Neto LG, Santos-Filho SD, Aizamaque E, Araújo HG, Bernardo-Filho M, Carvalho MGF, Soares CD Radiofrequency treatment induces fibroblast growth factor 2 expression and subsequently promotes neocollagenesis and neoangiogenesis in the skin tissue. Lasers Med Sci. 2017 Nov;32(8):1727-1736.
[5] Franco W, Kothare A, Ronan SJ, Grekin RC, McCalmont TH. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: feasibility studies. Lasers Surg Med. 2010 Jul;42(5):361-70.

1.2.3 – The use of thermal shock and its slimming effect

Ross Anderson describes the thermal shock process very well in his studies on cryolipolysis (2008). Fat cells are more sensitive to cold than the other cells in the skin. They crystalize around – 3 °C (26.6 °F) and when they go back to the normal body temperature (37 °C, i.e. 98.6 °F), we can observe a 20% lysis of the treated volume.

As a result of this finding, several recent studies mention the use of two processes, associating heat and cold for slimming. A 2016 study[6] on 10 subjects shows how effective the combination of cryolipolysis and radiofrequency is in the reducing fat and firming skin.

1.3 – Research tools

1.3.1 – Research methodology

- Fundamental bibliographic research.
- Bibliographic research on studies and scientific literature (Pub Med).
- Analysis of the bibliographic research results.

1.3.2 – Documentary/bibliographic research

Information sources

Bibliographic database:

- Medline (National Library of Medicine, USA);

Other sources:

- Websites of scientific societies qualified in the studied field.
- Bibliography of the selected articles and documents.

1.3.3 – Research strategies

Keywords:

The bibliographic research on PubMed was done on the following keywords:

- Cryolipolysis / Cryotherapy
- Thermotherapy / Thermal therapy/ Heat therapy
- Fat reduction
- Body contouring

[6] Few J, Gold M, Sadick N. Prospective Internally Controlled Blind Reviewed Clinical Evaluation of Cryolipolysis Combined With Multipolar Radiofrequency and Varipulse Technology for Enhanced Subject Results in Circumferential Fat Reduction and Skin Laxity of the Flanks. J Drugs Dermatol. 2016 Nov 1;15(11):1354-1358.

2 – Objectives of the study

The main objective of the Cryoskin 3.0 study is to evaluate the effectiveness of Cryoskin 3.0 on slimming of the abdominal area when following the protocol designed by Prodesign Plus (five 40-minute treatments, at the rate of one every 15 days).

3 – Type of study

3.1 – Description

It is an observational study on 16 patients spaced out over 3 months. The effectiveness criteria will then be statistically compared to establish the impact of the Cryoskin 3.0 protocol in slimming the abdominal circumference.

The number of patients included in this study was decided based on the latest ANSES[7] report on observational studies in the beauty field. They only consider studies involving at least 12 patients.

Study location and prescriber: Dr. Blanchemaison's medical practice, 113 avenue Victor Hugo – 75116 Paris.

The study comprises 2 visits, at Day 0 and Day 60.

- **Day 0**: baseline visit (effectiveness criteria)
- **Day 60**: final visit, after the completion of the 5-session protocol with Cryoskin 3.0, to evaluate effectiveness and side effects.

3.2 – Intermediary analysis

N/A.

3.3 – Evaluation Committees

N/A.

4. Selection of Study Subjects

Patients' enrollment is done by Dr. Blanchemaison. The participants are men and women wishing to reduce the fat mass on their abdominal area (love handles, belly, back).

[7] Agence Nationale de Sécurité Sanitaire, French counterpart to the FDA (translator note).

4.1 – Inclusion criteria

The inclusion criteria are the following:

- Subject age 18+ and under 70
- Waist circumference < 95cm for women and <102 cm for men
- Stable weight for 3 months before the start of the study

The doctor will note the medical history and habits of the patients when selecting each subject and before the study begins.

4.2 – Exclusion criteria

The exclusion criteria are the following:

- Subject age under 18 and over 70
- Patients who started a weight loss program before the start of the study and who did not want to stop
- Pregnant and breastfeeding women
- Patients with a chronic disease requiring an ongoing treatment

4.3 – End of protocol

The protocol includes five treatment sessions, with one every 15 days.
Study duration: 3 months.
Any patient not showing up for their planned sessions is excluded from the study (with a 3-day leeway).

5. Effectiveness criteria

5.1 – Hypodermis' thickness

Every patient will be submitted to a Doppler ultrasound 13 Mhz under the belly button in order to measure the thickness of the subcutaneous tissue (hypodermis) right before the start of the study and then after the completion of the 5-session protocol with Cryoskin 3.0. This Doppler ultrasound will allow to measure each subject's subcutaneous fat thickness.

5.2 – Weight, BMI and body fat percentage

Each patient will be weighed using a Tanita-brand BIA scale (bioelectrical impedance analysis), right before the start of the study and again at the end. This scale will automatically calculate the subject's weight, BMI and body fat percentage.

5.3 – Waistline

The waistline of the 16 subjects will be measured right before the start of the study, after each Cryoskin 3.0 treatment and after the completion of the 5-session protocol. Their waistline will

be measured using an automatic spooling tape measure on the navel (belly button) while the subject is standing, with legs shoulder-width apart.

The person doing the measurements will adjust measuring tape correctly without squeezing too much, as to not compress the underlying soft tissues.

The waistline will be measured at the end of a regular exhalation and within 0.5 cm.

The measurements will be done by the same person, and wherever possible, at the same time of the day.

5.4 – Digital pictures

Digital pictures will be taken just before the start of the study, before each treatment, and after the completion of the Cryoskin 3.0 protocol. Every time, 4 digital pictures will be taken:

- Front, legs shoulder-width apart, with arms up and hands behind the head.
- Right and left profile, legs shoulder-width apart, with arms up and hands behind the head.
- Back, legs shoulder-width apart, with arms up and hands behind the head.

The photographer will be standing one meter (3.3 feet) away from the subject.
The pictures will always be done by the same person and will only show the patient's abdomen and legs.

5.5 – Satisfaction Survey

Patients will fill out a survey at the end of the protocol to evaluate their satisfaction regarding the results and comfort level.

5.6 – Form to record adverse events and tolerability evaluation

Before each session, we will record any adverse events experienced by the patient to evaluate their tolerance of the Cryoskin 3.0 device and to guarantee a comprehensive patient monitoring.

Date of occurrence	Notified person	Event's nature	Severity	Follow-up and actions taken	Notified investigator's signature

6 – Subjects' safety

6.1 – Adverse events

6.1.1 – Definitions

Adverse event:

Any harmful and unwanted manifestation experienced by a participant to a clinical test, was it considered to be linked or not to the medical device studied and whatever the reason for that manifestation was.

Severe adverse event:

Any harmful and unwanted manifestation experienced by a participant to a clinical test, whatever the dose, which:

- Becomes life-threatening,
- Causes the patient's hospitalization or its extension,
- Causes permanent or significant disability or incapacity,
- Is linked to a birth defect,
- Is a medically significant event,
- Results in death.

6.1.2 – Data collection and transfer

Non-severe adverse event

Any non-severe adverse event occurring during the study, including during the wait periods between treatments, will be recorded on an adverse event report form included in the case report form.

The investigator will have to mention the date of the event, its severity, the possible curative treatments and the evolution. He will give his opinion on the possible causal link between the event and the treatment under study.

Severe adverse event

In case of a severe adverse event, the investigator must:

- Immediately **fill out** the severe adverse event report form;
- Sign and date the form then **send** it by fax to the study sponsor within 24 hours;
- Immediately (that same day) **call** the study sponsor, in case of death or life-threatening event;
- **Attach** the copy of all available results and exams with their date, providing the lab reference values along with the biological data.

6.1.3 – Follow-up on adverse events

The investigator must take any appropriate measures to ensure the patients' safety. He must especially follow-up on the evolution of any adverse event (clinical, biological, or other…) until the recovery or the stabilization of the patient's condition.

For every medically pertinent event (severe adverse event, drop-out from the study, biological defect, or other cases specified in the study protocol), the investigator must order any additional exam recommended in the protocol, and provide any results allowing a better case evaluation (additional test results, hospital or lab report).

6.2 – Lab tests
N/A.

6.3 – Specific instructions
N/A.

7 – Premature drop-out from the study

7.1 – Reasons for dropping-out

The subjects will be able to leave the study or stop the treatments, if they or the investigator decide so, at any moment and whatever the reason for leaving is.

7.2 – Follow-up procedure in case of early drop-out

Every drop-out from the study should be documented and the investigator will have to mention the reason.
In the case of patients who "disappear", the case report form will need to be filled until the last visit performed. The investigator will do their best to contact the subjects and learn their reason for leaving the study and the condition of the health.

7.3 – Consequences

The subjects who decide to leave the study will not be included into the study. Their identification number will not be used again.

8 – Study's progress

8.1 – Enrollment

The subjects will be chosen by Dr Blanchemaison.

Inclusion period: from February 2nd, 2018 to May 23rd, 2018

1 – The doctor makes sure the subject qualifies for the Cryoskin 3.0 protocol and fills out the inclusion form.

2 – He gives **the information letter** to the subject and gets written consent in two copies. (See Appendix #2: Information letter; Appendix 3: Consent form)

3 – The doctor delivers the file to the participant and keeps copies of the consent form and the inclusion form (Appendix 4: Inclusion form).

4 – The person to contact at the medical practice is **Dr Blanchemaison**.

8.2 – Subject identification

- Last name and first name: _____

- Inclusion number: └___┘ └___┘

- Birth date: └___┘ └___┘ / └___┘ └___┘ / └___┘ └___┘ └___┘ └___┘

- Gender: (F) or (M)

The inclusion number will serve as a patient ID throughout the clinical study.

8.3 – Cryoskin 3.0 session

The 5 sessions of Cryoskin 3.0 will be done at the rate of one every 15 days, at Dr. Blanchemaison's practice, 113, Avenue Victor Hugo – 75116 Paris.
For this study, the 5 sessions will proceed as follows:

- Every Cryoskin 3.0 session will last 34 minutes.
- The sessions will be free for the subjects. They will make appointments with the sponsor.
- The doctor in charge of the measurements, the digital pictures and the good execution of the protocol will be available to the patients.
- The beautician performing the Cryoskin 3.0 treatments will be available to the subjects.

At the start of each session, the doctor will gather information on any post-treatment undesirable event. He will also measure the abdominal circumference before and after the treatment and will take digital pictures prior to the session.

After those examinations, the beautician will position the patient and proceed with the Cryoskin 3.0 treatment. She will answer questions from the patient about the process.

The treatment will follow the steps of the abdominal slimming protocol:

1. Back: 2 minutes at 40 °C, i.e. 104 °F (smoothing and sliding motions to heat the area) and 13 minutes at -8 °C (17.6 F) then 2 minutes at 35 °C, i.e. 95 °F (very slow but constant circular motions, the handpiece always in contact with the skin; slight pinching of the skin with the free hand to create a skin fold). The target: love handles and localized fat deposits.
2. Front: 2 minutes at 40 °C, i.e. 104 °F (smoothing and sliding motions to heat the area) and 13 minutes at -8 °C (17.6 F) then 2 minutes at 35 °C, i.e. 95 °F (very slow but constant circular motions, the handpiece always in contact with the skin; slight pinching of the skin with the free hand to create a skin fold). The target: fat pad in the lower abdomen.

A session includes 34 minutes of treatment by the beautician and lasts 40 minutes overall.

8.4 – Study monitoring

8.4.1 – Study schedule

	Screening	Inclusion	Cryoskin 3.0 Sessions					Last visit
Visit	**0**	**1**						**2**
Week	**Week 0-N**	**0**	**1 – 8**					**8**
Day	**Day 0**	**Day 1**	**5 sessions of Cryoskin 3.0**					**Day 60**
Information - Consent	**X**	**X**						
Medical history		**X**						
Inclusion/exclusion criteria		**X**						
Doppler Ultrasound 13 MHz (subcutaneous tissue thickness)		**X**						**X**
Impedance analysis (BMI, weight, % body fat)		**X**						**X**
Abdominal circumference (waistline)		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Digital pictures		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Data collection on adverse effects			**X**	**X**	**X**	**X**	**X**	
Effectiveness evaluation (satisfaction survey)								**X**
General tolerability of the treatment								**X**
Researcher	**Dr Blanchemaison**							

8.4.2 – Control visits
Two control visits will be necessary:

Inclusion visit (Day 0)

- Subject selection according to the inclusion and exclusion criteria
- Explanation of the protocol and obtaining the patient's signed informed consent
- Data collection on the case report form:
  1. Waistline
  2. BMI, weight, fat mass percentage
  3. Thickness of the abdominal subcutaneous tissue
  4. Digital pictures

Final visit, at the end of the study (Day 60)

- Data collection on the case report form, with the same data as those recorded during the first visit
- Satisfaction survey
- General evaluation of the tolerability and comfort of the treatment

The results will be compared to offer relevant and objective conclusions on the effectiveness of Cryoskin 3.0.
Moreover, throughout the study, the doctor will collect data about potential undesirable events and concomitant treatments.

9 – Statistical analysis

9.1 – General statistical approach
The continuous variables will be described by: average, standard deviation, median value, minimum and maximum for every treatment group.
The categorical variables will be described by: number and percentage.
Every statistical test will be bilateral with a 5% level of significance.

9.2 – General convention
The baseline for the effectiveness parameters is the value collected on Day 0.

9.3 – Statistical analysis
The results of the measurements will be reported in the respective units of measurement.
Every calculation is done using the Microsoft Excel software, the data treatment showing:

- Series' **minimum values**
- Series' **maximum values**
- Series' **mean values**, calculated as follows:

$$m = \frac{\sum_1^N Vi}{N}$$

Where: **m** is the average value
N is the total study's headcount
Vi is the value of the parameter analyzed in accordance with **N**

The **percentage variations** between participant will be calculated as follows:

$$\text{var.}(\%)_i = \left(\frac{Txi - T0i}{T0i}\right) \times 100$$

Where:
Txi is the individual value of the parameter at the end (Day 60)
T0i is the individual value of the parameter at the start (Day 0)

The **average percentage variations** are calculated as follows:

$$\text{var.}(\%) = \sum_{1}^{N} var.(\%)\, i$$

The data are treated through a **standard deviation function** as dispersion indicator.

$$\sqrt{\frac{\sum (x-\bar{x})^2}{(n-1)}}$$

Where: *x* is the average sample's data and *n* is the sample's size.

Data are subjected to a unilateral Student's t-test to compare the paired data. The variation is considered as statistically significant when the value of *p* is $p<0.05$.

9.4 – Data collection and statistical analysis

The data to be collected are:

- Subcutaneous tissue thickness (hypodermis): before and after each session
- BMI, weight, fat mass %: at the inclusion visit and the last visit
- Abdominal circumference measurement: at the inclusion visit and the last visit
- Abdominal circumference measurement: before and after each session

The statistical analysis will apply to:

- Variation in hypodermis' thickness: before and after protocol
- Variation in BMI, weight, fat mass %: before and after protocol
- Variation in abdominal circumference measurement: before and after protocol
- Variation in abdominal circumference measurement: before and after each session

10. Ethical rules and regulatory references

10.1 – Applicable laws

The study will be conducted in compliance with:

• the Huriet Serusclat Law ("*Loi Huriet Serusclat*") n°88-1138 from December 20, 1988 protecting clinical study participants ;

• the Helsinki Declaration adopted by the 18th World Medical Assembly in 1964 and its amendments;

• the International Conference on Harmonisation recommendations regarding clinical studies;

• the European Directive 2001/20/CE;

• the « *Loi de santé publique* » (Public Health Act) from August 9, 2004 and its implementing Decree from April 26, 2006;

• the Clinical Best Practices ("*Bonnes Pratiques Cliniques*") revised by the November 24, 2006's decision;
• the DMOS Law ("*Loi Diverses Mesures d'Ordre Social*"), article L.4113-6 from the Public Health Code;
• the Data Protection Act (*"Loi Informatique et Libertés"*) n° 78-17 from January 6, 1978, modified by the Law n° 94-548 from July 1st, 1994.

10.2 – Information and patient consent
The goal and the study's methods will be explained to the patients before their participation in the study. The patient will give written consent on an information form and informed consent form.

11 – Study management

11.1 – Investigator's responsibilities
The investigator commits to carry out the study according to the protocol, the Clinical Best Practices and the applicable regulatory requirements.
The investigator commits to respect the protocol process, the treatment standards, the visit dates.
The investigator agrees to provide any requested information in the case report form with precision and accuracy, according to the provided guidelines.

11.2 – Sponsor's responsibilities
The study's sponsor is responsible, before the Public Health authorities, for insuring the good execution of the study in terms of ethics, respect of the protocol, truthfulness and validity of the data collected in the case report. The main task of the investigator and the sponsor is to maintain a high level of scientific ethics and to guarantee the technical and regulatory quality of the study at all times.

11.3 – Source documents
According to the Clinical Best Practices' recommendations, the investigator will have to check the accuracy of the case report's data, in comparison with the source documents.
The informed consent form will include a statement in which the patient gives permission to the sponsor's authorized representatives and to the Health authorities to directly access source data substantiating the data recorded in the case report form (patient's medical file, appointment calendar, original copy of lab exams). Those individuals, bound by professional secrecy, will not reveal or disclose the patient's identity nor his/her medical information.

11.4 – Use and storage of the case report forms and additional requests
It is the investigator's responsibility to fill the case reports with accuracy and care. Every case report form must be filled out in its entirety in a legible manner to ensure a precise interpretation of the data. He will need to use a black ballpen for the sake of clarity.

In case of correction, the data must be modified but not striked-out. The corrected data must be copied by the authorized person next to the former value, then signed and dated.
The data entry by the sponsor after receiving the case reports can produce additional requests. The investigator will have to answer those requests by confirming or changing the data in question. The requests and their answers will be added as appendices to the case report (or to the case report's copy) owned by the investigator and the sponsor.

12 – Administrative regulations

Data storage in the investigating center(s):
The investigator will keep all the documents pertaining to the study and will take every necessary measure to prevent their accidental or premature destruction. Those documents will be stored for the maximum duration allowed by the hospital or the private practice.
In compliance with the Clinical Best Practices and the law, the investigator will make sure that the patients' files and the entirety of the documents pertaining to the study are stored for at least 15 years after the end (or the interruption) of the study.
The investigator will keep case reports' copies, the paperwork, the participating patients list and their signed consent forms for at least 15 years after the end of the study.
The patients' files must be stored either by the investigator (private practice) or by the archive department of the hospital where he works.
A label indicating the patient's participation in a clinical study and the necessity to preserve all the documents in the patient's file for 15 years after the end of the study can be pasted on the file's cover.
Every center wishing to destroy those data must first inform Prodesign Plus.

13 – Non-disclosure
All materials, information and unpublished documents provided to the investigator (or to a society acting on his behalf), including the protocol, the case reports and the clinical investigator pamphlet, are the exclusive property of Prodesign Plus.
Those materials and information cannot be delivered or disclosed to a third party, in totality or partially, by the investigator or any person working under his authority, without prior written authorization from Prodesign Plus.
The investigator will need to consider any information, data, results, discovery, or reports as confidential (apart from the information legally required) and cannot disclose them to a third party without the prior written authorization from SFAS.

14 – Intellectual property
The sponsor holds the exclusive intellectual property of all data, results, reports, discoveries and any other information relative to the study. As a result, the sponsor reserves the right to use the data and the present report, as he sees fit, with or without comments or analysis.

Moreover, in case the study should produce patentable results, the investigator (or any person acting on his behalf in compliance with the local regulation) waives any right to apply a patent based on those results. The sponsor (or a person acting on his behalf) is the only one allowed to apply for a patent, at his own expense.

15 – Insurance

The company Prodesign Plus certifies they have taken out insurance for this study, in accordance with French legislation.

16 – Early interruption of the study or center shutdown

16.1 – Decided by SFAS

SFAS can stop the study or prematurely close a center in the following cases:

- The study's execution does not comply with the procedures defined when the protocol was approved (low enrollment, deviations from the protocol, data quality not guaranteed),
- Information on the product calls the benefit/risk ratio into question,
- The total number of patients is reached before the expected deadline,
- SFAS decision.

16.2 – Decided by the investigator

The investigator should notify SFAS and the investigator of his decision and explain its reason in writing.

16.3 – Decided by the sponsor

The sponsor should notify SFAS and the study's sponsor of his decision and explain its reason in writing.

16.4 – Consequences

In any case, the investigator will follow-up with the patients and ensure the final visit.

17 – STUDY SCHEDULE PER VOLUNTEER

T0	Clinical exam to enter the study and clinical scoring Measurements: weight, BMI, abdominal circumference Standardized pictures Doppler ultrasound Self-evaluation survey
Session 1	34 minutes of Cryoskin 3.0 treatment = 2 minutes at 40 °C (104 °F), 13 minutes at -3 °C (26.6 °F), 2 minutes at 35 °C (95 °F)
Sessions 2 and 3	= 2 minutes at 40 °C (104 °F), 13 minutes at -3 °C (26.6 °F), 2 minutes at 35 °C (95 °F)
Sessions 4 and 5	= 2 minutes at 40 °C (104 °F), 13 minutes at -3 °C (26.6 °F), 2 minutes at 35 °C (95 °F)
T1 (=T0 + 5 sessions)	Clinical exam to enter the study and clinical scoring Measurements: weight, BMI, abdominal belt circumference Standardized pictures Doppler ultrasound Self-evaluation survey Acceptability survey

18 – RESULTS ANALYSIS

The final analysis of the results concerned 16 subjects. None of the subjects left the study.

FUNCTIONAL CLINICAL TEST

Clinical signs

The details regarding the clinical monitoring can be found in the individual case reports (Appendix #4).

The presence of cellulite was monitored from the initial intake to the end of the 5-session protocol by the doctor in charge.

The functional and clinical signs have been examined and the severity of each manifestation has been evaluated using the following predefined scoring system:

1 no sign
2 very minor sign
3 minor sign
4 moderate intermediate sign
5 significant sign
6 very significant sign
7 major sign

The exam and functional signs studied were:
Cellulite aspect without pinching the skin
Cellulite aspect when pinching
Fat pad
Pain when pinching the skin

The results were analyzed by summing before and after scores and comparing averages.

Results regarding clinical signs (16 subjects)

Cellulite without pinching:

Average scores at the beginning of the study:

Belly 3.0
Average 3.0

This sign manifestation is *moderate*.

Average scores at the end of the study:

Belly 1.5
Average 1.5

On average, the manifestation of this sign scores between *minor and very minor*.

On that indicator, we can notice a positive change with a 50% reduction of the sign impact.

Cellulite when pinching:

Average scores at the beginning of the study:

Belly 4.4
Average 4.4

On average, this sign manifestation ranges between *very significant and significant*.

Average scores at the end of the study:
Belly 2.9
Average 2.8
On average, the manifestation of this sign scores right below *moderate*.

On that indicator, we notice a significant positive evolution, with a 36.6% reduction of the sign impact.

Fat pad
Average scores at the beginning of the study:
Belly 4.7
Average 4.7
On average, this sign manifestation ranges between *very significant and significant, closer to very significant.*

On that indicator, we notice a significant positive evolution, with a 26.7% reduction of the sign impact.

Average scores at the end of the study:
Belly 3.5
Average 3.4
On average, this sign manifestation ranges between *significant and moderate.*

On that indicator, we notice a significant positive evolution, with a 26.7 % reduction of the sign impact.

Pain when pinching the skin (16 subjects):
Average scores at the beginning of the study:
Belly 2.3
Average 2.4
On average, this sign manifestation is *moderate*.

Average scores at the end of the study:
Belly 1.0
Average 1.0
On average, this sign manifestation is *very minor.*

On that indicator, we notice a significant positive evolution, with a 57.7 % reduction of the sign impact.

Statistical analysis of the clinical signs

A Wilcoxon test (a non-parametric test used to compare 2 paired samples) was done to figure out if the averages recorded between T0 and T1, were statistically different.

Cellulite without pinching T0/T1	z = 3.180 p = 0.0015	significant difference
Cellulite with pinching T0/T1	z = 3.408 p = 0.0007	significant difference
Fat pads T0/T1	z = 3.059 p = 0.0022	significant difference
Pain when pinching T0/T1	z = 3.296 p = 0.0010	significant difference

There is a significant difference between T0 and T1 for every studied clinical signs, with a 50% reduction of cellulite without pinching, a 36.6% reduction with pinching, a 26.7% reduction of fat pads and a 57.7% reduction of pain when pinching.

Medical findings regarding clinical condition

Considering the studied criteria and their evolution, the overall conclusion in terms of clinical evolution provides the following results:

SLIMMING EFFECT

Identical condition – 9 subjects – 56.3%
Slight improvement – 3 subjects – 18.8%
Improvement – 3 subjects – 18.8%
Significant improvement – 1 subject – 6.3%

Therefore, the clinical exam shows an improvement for 43.8% of patients (whatever its degree), with a slimming effect driven by the entire method.

CONTOURING EFFECT

Identical condition – 2 subjects – 12.5%
Slight improvement – 8 subjects – 50.0%
Improvement – 4 subjects – 25.0%
Significant improvement – 2 subjects – 12.5%

Therefore, the clinical exam shows an improvement for 87.5% of patients (whatever its degree), with a contouring effect driven by the entire method.

EFFECT ON SKIN QUALITY

Identical condition – 0 subject
Slight improvement – 1 subject – 6.3%
Improvement – 14 subjects – 87.5%
Significant improvement – 1 subject – 6.3%

Therefore, the clinical exam shows an improvement of the skin quality in terms of appearance (whatever its degree), driven by the entire method for 100% of patients.

Clinical tolerability (Appendix #10)

Cryoskin 3.0
Very good tolerability in 15 cases, namely 93.8%.
Moderate tolerability in 1 case, namely 6.2%
Subject #8: lack of comfort (hard mattress) during the first 2-3 sessions; no need to interrupt the sessions.

Self-evaluation
The volunteers' self-evaluation on their body's evolution as a result of the treatment was assessed through a survey delivered by the psychometric device PS24 (PSYCHO-LOG 24^{R}).

The answers were given in percentage scale, i.e. from 0 to 100, the answers ranging between:

0 = none to 100 = significant

or

0 = no to 100 = yes

The results are:

1 – What is the size of the fat pad on your waist?

From 0 = none to 100 = significant
Before the treatment, the average score is 74.9
After the treatment, the average score is 49.9
There is a 33.3% reduction.

2 – What is the size of the fat pad on your belly?

From 0 = none to 100 = significant
Before the treatment, the average score is 72.7
After the treatment, the average score is 47.8
There is a 34.2% reduction.

3 – How prominent is the cellulite on your belly?

From 0 = none to 100 = significant
Before the treatment, the average score is 63.6

After the treatment, the average score is 44.2
There is a 30.5% reduction.

4 – Is your skin smooth to the touch?
From 0 = no to 100 = yes
Before the treatment, the average score is 62.5
After the treatment, the average score is 73.4
There is a 17.4% increase.

5 – Do you like your silhouette?
From 0 = no to 100 = yes
Before the treatment, the average score is 17.9
After the treatment, the average score is 44.3
There is a 147.0% increase.

6 – Do you feel good about yourself?
From 0 = no to 100 = yes
Before the treatment, the average score is 42.2
After the treatment, the average score is 53.4
There is a 26.7% increase.

7 – Does your skin have a firm/good appearance?
From 0 = no to 100 = yes
Before the treatment, the average score is 53.6
After the treatment, the average score is 62.2
There is a 16.1% increase.

8 – Is your waistline slim?
From 0 = no to 100 = yes
Before the treatment, the average score is 34.3
After the treatment, the average score is 54.7
There is a 59.4% increase.

9 – Is your belly flat?
From 0 = no to 100 = yes
Before the treatment, the average score is 18.4
After the treatment, the average score is 36.6
There is a 99.0% increase.

10 – Do your clothes feel tight?
From 0 = no to 100 = yes
Before the treatment, the average score is 60.1

After the treatment, the average score is 44.2

There is a 26.4% reduction.

11- Would you feel comfortable wearing a swimsuit?

From 0 = no to 100 = yes

Before the treatment, the average score is 34.5

After the treatment, the average score is 52.1

There is a 51.1% increase.

Statistical analysis of the self-evaluation

A Wilcoxon test (a non-parametric test used to compare 2 paired samples) was done to figure out if the averages recorded between T0 and T1, were statistically different.

Waist's fat pad	z = 3,439 p = 0,0006	significant difference
Belly's fat pad	z = 3,408 p = 0,0007	significant difference
Belly's cellulite	z = 3,237 p = 0,0012	significant difference
Smooth skin	z = 2,172 p = 0,0299	significant difference
Silhouette	z = 3,233 p = 0,0012	significant difference
Feeling good	z = 1,761 p = 0,0783	insignificant difference
Firm skin	z = 1,577 p = 0,1148	insignificant difference
Narrow waist	z = 2,668 p = 0,0076	significant difference
Flat belly	z = 2,584 p = 0,0098	significant difference
Tight clothes	z = 1,817 p = 0,0691	insignificant difference
Swimsuit	z = 2,560 p = 0,0105	significant difference

Therefore, we notice a statistically significant difference for the following self-evaluated signs:

33.3% reduction of fat pad on the waist

34.2% reduction of fat pad on the belly

30.5% reduction of the belly cellulite

The skin is considered smoother/softer, with a 17.4% improvement

The silhouette is preferred, with a 147.0% improvement

The waistline is considered slimmer, with a 59.4% improvement

The belly is considered flatter, with a 99.0% improvement

Wearing a swimsuit feels more comfortable, with a 51.1% improvement

BIOMETRICAL MEASUREMENTS

Measurements

Using the measurements taken before and after the 5 treatments on two different parts of the belly, an individual and an overall average were calculated.

The results for the 16 subjects are the following:

T0 mean value 97.2 cm (38.27 in)

T1 mean value 92.5 cm (36.4 in)

There is a 4.7 cm reduction (1.85 in), which represents 4.83% overall, the maximum reduction reaching 8.5 cm (3.34 in).

If we look at the difference between T0 and T1 for the 15 subjects for whom there was a reduction (even if small), the average reduction for them is 5.8 cm (2.28 in), i.e. 5.96%.

Statistical study on measurements

A Wilcoxon test on paired samples was done to figure out if the measurement averages recorded between T0 and T1 for the 16 subjects were statistically different.

T0/T1 z = 0,879 p = 0,3794 insignificant difference

The difference in mean value for the measurements between T0 and T1 shows a statistically insignificant difference.

The same statistical calculation was applied to the 15 responsive subjects:

T0 / T1 z = 2,803 p = 0,0051 significant difference

If you consider the 15 responsive subjects, there is a statistically significant difference, i.e. a 5.96% reduction in the waist circumference (waistline).

Weight and body fat

If you consider the mean values at T0 and T1 for the weight and body fat, we notice a weight reduction for the 16 subjects.

The results are the following:

T0

Average weight 67.2 kg (148 lbs)

Fat mass 22.8 kg (50.26 lbs)

Lean mass 44.4 kg (97.88 lbs)

T1

Average weight	66.5 kg (146.6 lbs)
Fat mass	22.5 kg (49.6 lbs)
Lean mass	44.0 kg (97 lbs)

Difference between T0 and T1 in grams:

Average weight	700 grams (1.54 lbs)
Fat mass	300 grams (0.66 lbs)

The maximum weight loss recorded is 5.5 kg (12.12 lbs), including 4.4 kg (9.70 lbs) of fat mass.

The weight loss breakdown in the group is the following:

Weight gain	2 subjects
Stable weight	2 subjects
Weight loss < 1kg (2.20 lbs)	4 subjects
Weight loss between 1 kg and 1.9 kg (4.18 lbs)	4 subjects
Weight loss between 2 kg and 2.9 kg (6.39 lbs)	3 subjects
Weight > 3kg (6.61 lbs)	1 subject

If we measure the weight loss of the 8 significantly responsive subjects (weight loss > 1kg), i.e. half of the group, we record an average weight loss of 2.7 kg (5.95 lbs).

Statistical study on weight and BM

A Wilcoxon test on paired samples was done to figure out if the average weight losses recorded between T0 and T1 were statistically different for the 12 responsive subjects.

Total weight:

T0/T1 z = 1,287 p = 0,1981 insignificant difference

The difference in mean value for the weight between T0 and T1 does not show a statistically significant reduction.

The group of the most responsive subjects is insufficient (5 subjects) to allow a statistical analysis.

PSYCHO-SENSORY ACCEPTABILITY

The psycho-sensory acceptability has been evaluated with a survey after the 5 sessions. The questions dealt with the organoleptic qualities of the cosmetic products used, with the conditions of use of the device and with the estimated effect of the Cryoskin 3.0 method.

The buying interest and the opinion on other methods used previously for the same purpose were also evaluated. Finally, the subjects were asked the method's main flaw and main quality.

Evaluation survey

1 – I liked the initial heating of the area.

Completely agree	94%
Agree	6%
Neither agree, nor disagree	0%
Disagree	0%
Completely disagree	0%

The heating phase at the beginning of the session is judged positively in 100% of cases.

2- The feeling when the handpiece is applied on the skin is pleasant.

Completely agree	63%
Agree	31%
Neither agree, nor disagree	6%
Disagree	0%
Completely disagree	0%

The feeling during the application of the handpiece is judged positively in 94% of cases.

3 – The feeling when the handpiece is moving is pleasant.

Completely agree	75%
Agree	19%
Neither agree, nor disagree	0%
Disagree	0%
Completely disagree	6%

The feeling when the handpiece is moving is judged positively in 94% of cases.

4 – The use of gel is a plus.

Completely agree	88%
Agree	6%
Neither agree, nor disagree	0%
Disagree	6%
Completely disagree	0%

The use of gel is judged positively in 94% of cases.

5 – The posture during the session is comfortable.

Completely agree	50%
Agree	38%
Neither agree, nor disagree	0%
Disagree	13%
Completely disagree	0%

The posture during the session is judged positively in 88% of cases but negatively in 13% of cases.

6 – The treatment session is pleasant.

Completely agree	81%
Agree	19%
Neither agree, nor disagree	0%
Disagree	0%
Completely disagree	0%

The treatment session is judged positively in 100% of cases.

7 – I think the length of each treatment (40 minutes) is appropriate.

Completely agree	69%
Agree	25%
Neither agree, nor disagree	0%
Disagree	6%
Completely disagree	0%

The treatment's length is judged positively in 94% of cases.

8 – The total number of sessions (5) is appropriate.

Completely agree	56%
Agree	25%
Neither agree, nor disagree	19%
Disagree	6%
Completely disagree	0%

The total number of sessions is judged positively in 81% of cases.

9 – The cold temperature is bearable overall.

Completely agree	56%
Agree	38%
Neither agree, nor disagree	0%
Disagree	6%
Completely disagree	0%

The cold temperature is judged positively in 94% of cases.

10 – After the session, I feel relaxed.

Completely agree	81%
Agree	6%
Neither agree, nor disagree	13%
Disagree	0%
Completely disagree	0%

The relaxed feeling after the session is judged positively in 87% of cases and 13% of subjects have no opinion.

11 – After the session, I feel more energetic.

Completely agree	81%
Agree	6%
Neither agree, nor disagree	13%
Disagree	0%
Completely disagree	0%

After the session, 87% of subjects feel more energetic. 13% of subjects have no opinion.

12 – After the session, I am in a better mood.

Completely agree	50%
Agree	31%
Neither agree, nor disagree	13%
Disagree	6%
Completely disagree	0%

After the session, 81% of subjects are in a better mood. 13% of subjects have no opinion.

13 – I feel like the treatments improved the quality of my skin.

Completely agree	44%
Agree	50%
Neither agree, nor disagree	6%
Disagree	0%
Completely disagree	0%

After the entire protocol, 94% of subjects think the quality of their skin has improved. 6% of subjects have no opinion.

14 – I think the length of each complete session is appropriate.

Completely agree	56%
Agree	38%
Neither agree, nor disagree	0%
Disagree	6%
Completely disagree	0%

The length of each complete session is judged positively in 94% of cases.

15 – I think the treatment made me slimmer.

Completely agree	25%
Agree	6%
Neither agree, nor disagree	56%
Disagree	13%
Completely disagree	0%

After the entire protocol, 31% of subjects think they have become slimmer and 56% of them have no opinion.

16 – I think my overall silhouette improved.

Completely agree	31%
Agree	44%
Neither agree, nor disagree	13%
Disagree	13%
Completely disagree	0%

After the entire protocol, 75% of subjects think their silhouette has improved. 13% of subjects have no opinion.

17 – I am satisfied overall with the results achieved thanks to this method.

Completely agree	50%
Agree	44%
Neither agree, nor disagree	6%
Disagree	0%
Completely disagree	0%

After the entire protocol, 94% of subjects think their silhouette has improved. 6% of subjects have no opinion.

18 – The dietary advice given at the beginning helped me.

Completely agree	19%
Agree	50%
Neither agree, nor disagree	31%
Disagree	0%
Completely disagree	0%

The dietary advice is judged positively in 69% of cases and 31% of subjects have no opinion.

19- I would like to do regular treatments using this method (if possible).

Completely agree	75%
Agree	13%
Neither agree, nor disagree	13%
Disagree	0%
Completely disagree	0%

88% of subjects would like to do regular treatments with this method. 13% of subjects have no opinion.

20 – The results are worth my time investment.

Completely agree	50%
Agree	31%
Neither agree, nor disagree	13%
Disagree	6%
Completely disagree	0%

After the entire protocol, 81% of subjects think the time spent was worth the results they got. 13% of subjects have no opinion.

21 – I regret having to stop.

Completely agree	81%
Agree	6%
Neither agree, nor disagree	6%
Disagree	6%
Completely disagree	0%

After the entire protocol, 87% of subjects regret having to stop and 6% of subjects have no opinion.

22 – I did not experience any discomfort during the sessions.

Completely agree	69%
Agree	25%
Neither agree, nor disagree	0%
Disagree	6%
Completely disagree	0%

94% of subjects experienced no discomfort during the sessions.

Wish to continue and comparative review

Wish to continue

15 subjects answered "YES, right away", i.e. 93.8%

1 subject answered "NO", i.e. 6.2% (because of insufficient results on cellulite)

Comparison with previously tested methods (on 15 subjects out of 16, one having no opinion)

9 subjects found the Cryoskin 3.0 method "better"

2 subjects found the Cryoskin 3.0 method "a little better"

9 subjects found the Cryoskin 3.0 method "identical"

9 subjects found the Cryoskin 3.0 method "worse"

One subject found the method worse than long-wave infrared treatment associated with physical therapy.

Another found it worse than CelluM6.

Overall, 73.3% of subjects find the method better than those previously used.

Main quality / main flaw

The comments regarding qualities and flaws of the studied method, and the individual overall rating, are recorded on the individual case report forms (***Appendix #6***) and in the summary tables (***Appendix #17***).

10 subjects mention the relaxing and anti-stress effect,

4 subjects mention the contouring effect,

2 subjects mention the slimming effect,

4 subjects mention the effect on skin.

10 out of 16 subjects did not see any weakness to the method, apart from a few remarks regarding comfort.

When it comes to the overall rating, the question was:
“If you consider the overall method, which rating would you give on a scale from “1=very bad” to “10=excellent”?”
The average rating is 8.4, which means above “GOOD”.
Keep in mind that this average value was obtained despite the fact that the volunteer #5 gave a rating inferior to 5.

MEASUREMENT OF THE SUBCUTANEOUS FAT TISSUE THICKNESS

GENERALITIES

Often used in obstetric, sport medicine, urology or emergency medicine, the Doppler ultrasound has numerous purposes/applications.
In this study, this technique was used to measure the thickness of the subcutaneous fat tissue around the belly and the front of the thighs.

DEVICE AND MEASUREMENT METHODS

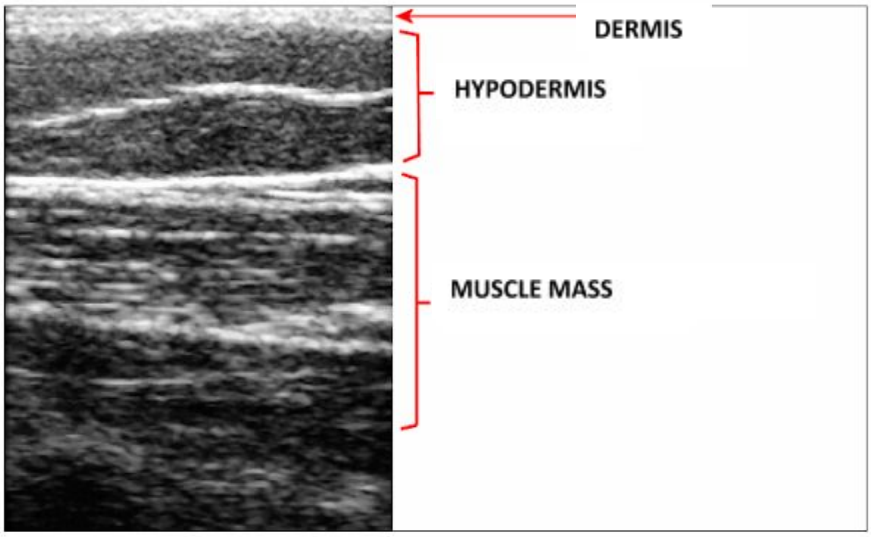
The SONOSCAPE Ultrasound scanner

The device used for this study is a SONOSCAPE Ultrasound scanner with a 7.5 Mhz linear probe. The ultrasound allows a high definition observation of the examined area up to 60 mm (2.4 in) under the skin (dermis).
Thanks to its high-frequency use, the ultrasound reveals through ultrasound images the anti-cellulite effects of cosmetic treatments.

For a precise analysis, the 7.5 Mhz linear probe/sound allows deep penetration into subcutaneous tissues and produces ultrasound scans (images and measurements) revealing the thickness of the subcutaneous fat tissues (hypodermis), between the muscular aponeurosis, the dermis and the skin surface.

Measurement methodology

The thickness of the subcutaneous fat tissue around the belly was measured at T0 and T1 to show the Cryoskin 3.0 program's effect on volunteers, according to the predefined objectives. A precise tracking system insured the measurement was done on the same spot each time.
The measurement is done using a low-frequency ultrasound unit. The produced images are of a vertical cross-section of the skin, to a depth of approximately 5cm (1.97 in) and a length of 4 cm (1.57 in). The analyzed area is the belly, where 3 specific areas appear: the dermis, the hypodermis and the muscles.



To measure the depth of the hypodermis, we identify divisions between those three areas. Two preprocessing/pre-treatments of the image are applied to make the divisions clearer.

- Use of a median filter to reduce the image noise level.

The median filter is very effective in canceling the image noise and making grayscale pictures clearer, including ultrasound images. It works by replacing one pixel value with the median value of all its surrounding pixels. That way the pulsed pixels are erased, and the divisions appear as the most significant information on the image.

ORIGINAL IMAGE

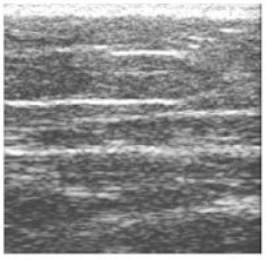
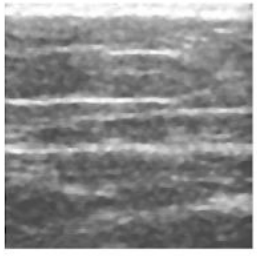


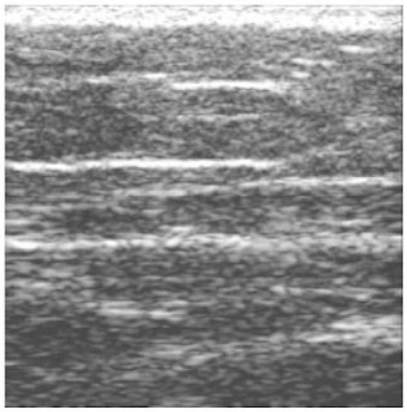
IMAGE WITH MEDIAN FILTER



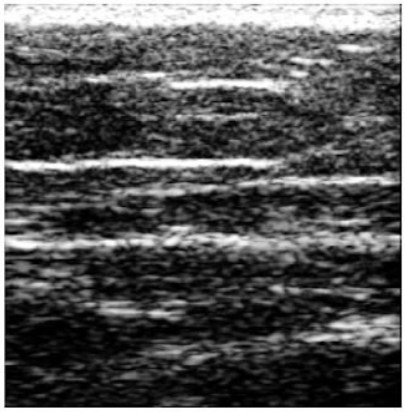
- Contrast improvement

The image data are coded in 256 grey levels. Yet only some values are relevant. To better highlight the white parts (which represent the divisions we are looking for), we improve the contrast by stretching the distribution histogram of the grey tones.

Unfiltered image



Sharper contrast

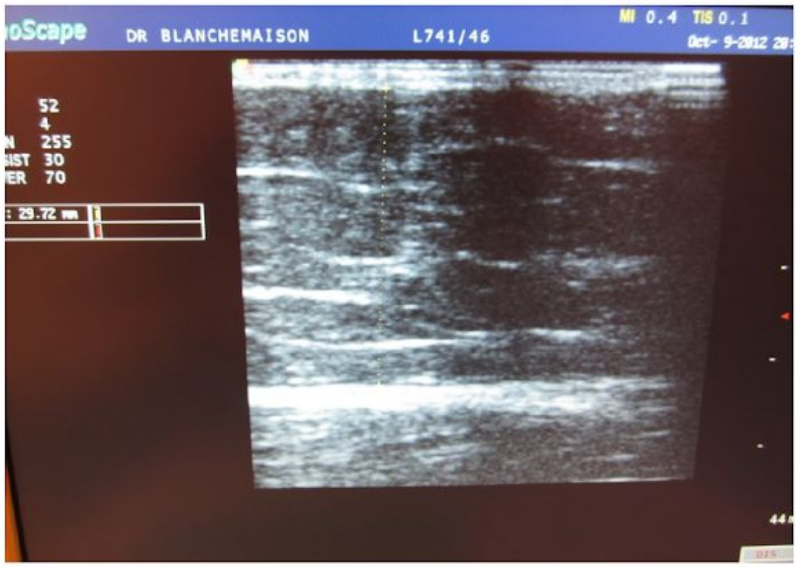


The combination of the two editing treatments gives the following result: a noiseless image where the relevant division lines stand out.

Measurement

The measurement method requires to measure the length of several sections linking dermis and muscles. This method is quick and effective. We take 5 measurements per image and we calculate the average.

The images are ultrasound screenshots. The screen display includes a scale to be able to take measurements in millimeters:



The digital pictures can be measured in pixels, as well as the scale figure beside each screenshot. This graduated scale allows drawing correspondence between pixels on the image and real measurements in millimeters.
Thus the 5 centimeters scale (5 graduations) corresponds to 325 pixels on the image. A simple ratio allows to convert pixels into millimeters.

For example:
On the above image, the fat tissue thickness measures 106 pixels, i.e. 1.61 cm (0.63 in):
(106 pixels*5cm / 235 pixels = 1.61 cm.

Data automation thanks to digital editing and computerized measurements provide more precise measurements because it produces more sharper measurements.
The multiplication of measurements gives us more reliable results by averaging several measurements on different image's parts.
Thus, the final result is objective and cannot be influenced by an arbitrary choice regarding the measured area.

RESULTS ANALYSIS

Measurement modalities
The chosen area on the belly is located midway between the navel and the anterior superior iliac spine.
We chose this specific area because in that spot the thickness of the subcutaneous fat tissue is usually comprised between 15 mm (0.59 in) and 35 mm (1.38 in) for non-obese subjects. Furthermore, the underlying layer of muscle fiber (muscle fascia) is made more evident.

Results
Based on the measurements of the subcutaneous fat tissue thickness taken before and after each Cryoskin 3.0 treatment, we recorded 5 measurements on each ultrasound image at T0 and T1. We then calculated an individual and a collective average.
The results for the 16 analyzed subjects are:
T0 mean value 17.15 mm (0.67 in)
T1 mean value 13.90 mm (0.55 in)
On average, there is a 3.25 mm (0.13 in) reduction, i.e. 18.96%, the maximum reduction reaching 7.96 mm (0.31 in).
If we consider the difference between T0 and T1 for the 15 subjects who reached a reduction >2 mm (0.08 in), the average reduction is 4.35 mm (0.17 in), i.e. 24.71%.

Statistical study on ultrasound measurements

A Wilcoxon test on paired samples was done to figure out if the averages recorded between T0 and T1 were statistically different for the entire group (16 subjects).

T0 / T1 z = 3,464 p = 0,0005 significant difference

The difference in ultrasound measurements' mean values between T0 and T1 shows a statistically significant 18.96% reduction of the subcutaneous fat tissue thickness for the entire group.

For the 15 responsive subjects, we applied the same calculation:

T0 / T1 z = 2,934 p = 0,0033 significant difference

The difference in ultrasound measurements' mean values between T0 and T1 shows a statistically significant 24.71% reduction of the subcutaneous fat tissue thickness for that specific group.

The ultrasound measurements show a statistically significant reduction of the mean values for the subcutaneous fat tissue thickness of the belly for the entire group. On average, there is 3.25 mm (0.13 in) reduction, i.e. 18.96%, with a maximum reduction of 7.96 mm (0.31 in) for one subject.

For the 15 responsive subjects (showing a reduction of at least 2 mm, i.e. 0.08 in), the average reduction is 4.35 mm (0.17 in), i.e. 24.18%.

The ultrasound proves therefore the effects of the Cryoskin 3.0 method. Combined with the clinical and biometrical results recording in the initial report, it validates the use of this method for body treatments and the claim of a "contouring effect on the silhouette" in particular.

18 – COMMENTS AND CONCLUSIONS

First, we must emphasize the originality of the CRYOSKIN 3.0 device: it works by using a mobile, heated then chilled, handpiece on the skin, which differentiates this method from those using a static suction device. A slow but constant motion associated with a specific manual manipulation allows to treat the subcutaneous tissue in depth and prevents any risk of frostbite than can be caused by a static method.

This technology, combined with the initial heating of the area, intensifies the thermal shock while preventing any risk of skin damage. The results are similar to the suction method but without side effects.

Moreover, each body part can be treated: belly, inner and outer thighs, knees, ankles, arms, chin, face contour.

The study of the slimming and reshaping effectiveness of the Cryoskin 3.0 method was conducted according to the investigative methods defined in the study protocol designed by the study sponsor, PRODESIGN PLUS, and Dr Philippe Blanchemaison, Scientific Director of the "Société Française d'Accréditation Santé", aka SFAS (**French Society for Health Certification**).

This study was conducted under strict medical supervision and dealt with the clinical effectiveness and the tolerability (in the clinical meaning of the word) of the Cryoskin 3.0 protocol.

The clinical evaluations were done by the doctor in charge of the study.

The self-evaluated effects, the acceptability and the conditions of use were evaluated using a self-evaluation survey.

The biometrical measurements, taken before entering the study and after 10 weeks, i.e. 5 treatment sessions, were comprised of:

- Abdominal circumference (waistline) measurements;
- Weight and body mass, with impedance measuring device calculating lean and fat body mass;
- Ultrasound measurement of the subcutaneous fat tissue thickness
- Standardized digital pictures of the fatty areas (front and back)

The study lasted 10 weeks per volunteer, at the rate of one session every 15 days.

Results analysis of the **functional clinical test under medical supervision, with self-evaluation, measurements and ultrasounds**, concerned 16 subjects, presenting the characteristics described in chapter "Inclusion criteria".

The clinical analysis shows a statistically significant difference on every tracked sign:

- **The cellulite (without pinching) is reduced by 50%**
- **The cellulite (with pinching) is reduced by 36.6%**
- **The fat pads are reduced by 26.7%**
- **The pain when pinching is reduced by 57.7%**

The overall medical assessment on the complete method is that there is:

- A slimming effect, with varying degrees, in 43.8% of cases;
- A reshaping effect, with varying degrees, in 87.5% of cases;
- Skin improvement, with varying degrees, in 100% of cases.

The self-evaluation *(direct consumer's review)* shows a statistically significant difference on the following signs:

- Waist fat pad is reduced by 33.3%
- Abdominal fat pad is reduced by 34.2%
- The cellulite on the belly is reduced by 30.5%
- The skin is considered smoother, with an improvement of 17.4%
- The silhouette improved, with an improvement of 147.0%
- The waistline is considered slimmer, with an improvement of 59.4%
- The belly is considered flatter, with an improvement of 99.0%
- Wearing a swimsuit feels more comfortable, with an improvement of 51.1%

The main unappealing cosmetic aspects typical of cellulite show a positive improvement after 5 sessions, according to the volunteers.

The allergenic tolerability was always good, and we did not record any side effects while using the Cryoskin 3.0 method.

The clinical tolerability of the device is excellent for the 16 volunteers, i.e. in 100% of cases. No session had to be interrupted.

The abdominal circumference measurements show a statistically significant difference in mean values for the entire group.

On average, there is a 4.7 cm (1.85 in) reduction, i.e. 4.83% for the group, the maximum reduction reaching **8.5 cm (3.35 in)**.

If we look at the difference between T0 and T1 for the 15 responsive subjects, the average reduction for that group is 5.8 cm (2.28 in), i.e. 5.96%.

The ultrasound measurements show a statistically significant difference in mean values of the subcutaneous fat tissue thickness for the entire group (16 subjects). On average, there is a 3.25 mm (0.13 in) reduction, i.e 18.96%, with a maximum reduction of **7.96 mm (0.31 in)** for one subject.
For the 15 subjects showing a 2 mm (0.08 in) or more reduction, the statistically significant reduction of the fat tissue thickness is, on average, 4.35 mm (0.17 in), i.e. 24.18%.

The ultrasound proves therefore the effects of the Cryoskin 3.0 method. Combined with the clinical and biometrical results recording in the initial report, it validates the use of this method for body treatments and the claim of a "reshaping and contouring effect on the silhouette" in particular.

The weight and body mass measurements do not show statistically significant difference between T0 and T1. On average, there is a 700 grams (1.54 lbs) weight loss.

The maximum recorded weight loss is 5.5 kg (12.12 lbs), including 4.4 kg (9.70 lbs) of fat mass.

The weight loss breakdown in the group is the following:

Weight gain	2 subjects
Stable weight	2 subjects
Weight loss < 1kg (2.20 lbs)	4 subjects
Weight loss between 1 kg and 1.9 kg (4.18 lbs)	4 subjects
Weight loss between 2 kg and 2.9 kg (6.39 lbs)	3 subjects
Weight > 3kg (6.61 lbs)	1 subject

If we measure the weight loss among the 8 most responsive subjects (weight loss > 1kg), i.e. half of the group, we reach an average of 2.7 kg (5.95 in).

The psycho-sensory acceptability is very satisfactory for the entire method since 94% of volunteers are satisfied with the method, and 88% of them would like to engage in regular treatments.

It should be noted that 81% of volunteers judge that their time investment was worth the results achieved, with 94% of them noticing improvement of the skin, 75% a silhouette reshaping and contouring effect and 31% a slimming effect. 87% of the volunteers also acknowledged the relaxing effect of the method.

We also notice that 15 of the 16 subjects, i.e. 93.75% of the group, wants to continue using this type of method and that 15 subjects think it is more effective than other methods used previously with the same purpose.

This study, whose objective was to evaluate the effectiveness of a new slimming technique based on the use of the Cryoskin 3.0, demonstrated primarily a reshaping and contouring effect, in most volunteers. The reduction of the unappealing cellulite aspect and the improvement of skin quality were significant.

Relevant biometrical methods, combined with a clinical study, conducted under strict medical supervision, validated the use of the Cryoskin 3.0 method for body treatments and the claim of a "reshaping and contouring effect on the silhouette", in the context of this study protocol.

The results recorded in the current report comply with the study protocol and their interpretation was based on current scientific knowledge.