ARTEMIS.

Clinical studies + MOA: Shape treatments

(These treatments are included on Neveskin™ Classic, Neveskin™ Duo, and Neveskin™ Ultra devices)

Agenda.

01. Introduction
02. Safety + efficacy study
03. Mechanism of action study
04. Key highlights + takeaways
05. Study credits

Introduction

INTRODUCTION

Clinical studies: Shape treatments

- The wait is over! After three years, our clinical studies outlining the safety, efficacy, and mechanism of action (MOA) of the Shape protocol have been completed.
- This protocol is found on on Neveskin™ Classic, Neveskin™ Duo, and Neveskin™ Ultra devices.
- Artemis carried out these clinical studies in collaboration with a leading dermatological clinical research organization (CRO), and Artemis Chief Medical Officer, Dr. Sach Mohan - with very exciting results.
- 2 studies were completed:
    - #1: Safety and efficacy (treatment risk profile + results)
    - #2: Mechanism of action (how the treatment works)
- This deck will summarize the findings and key outcomes from these studies.

Safety + efficacy study

FINDINGS & INTERPRETATION

SAFETY + EFFICACY STUDY

Introduction.

- This study was carried out by Cutest Systems LTD, a leading dermatological clinical research organization (CRO).
- Ethics Committee and Regulatory approval for the study was obtained from Reading Independent Ethics Committee.
- This study was divided into two parts: **safety** and **efficacy**.
    - Safety study objective: to confirm the safety profile of the protocol both when applied as directed and when applied at a 1.5x duration (i.e. user error/not as directed).
    - Efficacy study objective: to confirm protocol efficacy when applied as directed.
- 100 participants completed this study.
    - Participant demographics:
        - 20-70 years old (46 years old as mean age)
        - 93% were female participants, 7% were male participants
        - BMI 25-40 (32 as mean BMI)
- This study tested both static and manual Shape treatments applied to the abdomen and thighs.

PART A: SAFETY STUDY

Safety study design.

100 participants completed the safety portion of this study:

- 50 received 2 manual treatments (30 receiving the recommended treatment, 20 receiving 1.5x treatment time).
- 50 received 2 static treatments (30 receiving the recommended treatment, 20 receiving 1.5x treatment time).

Clinical markers were assessed on the skin at the treatment sites and non-treatment sites both prior to and immediately following the treatments, with the participants returning 24 hours after treatment for repeat measurements.

The clinical assessments were measured and interpreted using both clinical grading and biophysical measurements including:

- Clinical grading of skin erythema (redness caused by inflammation), edema (swelling caused by trapped fluid), dryness, and any other adverse effects.
- Chromometer (skin color).
- High frequency ultrasound imaging (depth, density, and structure).
- In vivo confocal microscopy (non-invasive ‘optical biopsy’ of morphology and dynamic characterization of skin structures).
- Pedal blood flow (to demonstrate that there was no systemic change).
- Skin caliper.
- Circumference.
- Digital photography of the skin.
- Participant questionnaire for self-assessment including statements like:
    - My skin feels dry.
    - My skin feels irritated.
    - My skin feels sensitive.

PART A: SAFETY STUDY

Safety study findings + interpretation.

Findings from the safety study showed:

- No changes in erythema, edema, or blood flow at the remote pedal site that would indicate a systemic effect of the treatment beyond the target site.
- Ultrasound measurements showed no structural changes to tissues that would indicate trauma.
- Measurements of skinfold thickness using calipers showed no gross changes.

These findings were consistent across both the standard treatment time and 1.5x treatment time for both the manual and static treatments (which was designed to test user error).

The participant questionnaire for self-assessment demonstrated that the treatment was very well-tolerated, with only minor negative feedback on the 1.5x dose of the static treatment.

These findings show that **the treatments have a very high safety profile and low risk when applied to clients as intended**, as demonstrated by the statement to the right.

Clinical interpretation by Cutest LTD clinical research organization:

“From the safety study, we conclude that both the manual and static treatment modes are safe for [clients] when administered using the standard parameters.

We conclude that the device has very high safety for [clients] and is unlikely to cause any significant adverse effects when used as intended.”

PART B: EFFICACY STUDY

Efficacy study design.

100 participants completed the efficacy portion of this study:

- 50 received a series of 5-10 manual treatments (30 on the abdomen, 20 on the thighs).
- 50 received a series of 5-10 static treatments (30 on the abdomen, 20 on the thighs).

The efficacy study included both safety clinical assessment as well as efficacy assessments. The following safety metrics were measured:

- Clinical grading of skin erythema, edema, dryness, and any other adverse effects.

In terms of efficacy measurements, the following were measured throughout the participants' course of treatments:

- High frequency ultrasound (to determine impact of the treatment on skin structure).
- Participant BMI (to determine whether results were impacted by weight changes throughout the study).
- Circumference (both pre and post each treatment).
- Skin caliper.
- Digital photography of the treated area.
- Participant questionnaire for self-assessment (same as the safety study) including statements like:
    - My skin feels dry.
    - My skin feels irritated.
    - My skin feels sensitive.

PART B: EFFICACY STUDY

Efficacy study findings + interpretation.

Findings from the efficacy study showed:

- No cumulative negative effects were noted following repeat treatments.
- Mild, transient erythema was recorded but changes were minimal and consistent with contact on the skin of the device and considered clinically insignificant.
- Skin caliper data + before and after images demonstrate clearly that there were significant changes in circumference measured after a course of treatments.
    - The statistically significant changes were seen at later treatments, indicating that a course of treatments is required to achieve clinically significant changes in circumference and body appearance.

The study showed a course of 5-10 treatments led to a statistically significant average reduction in circumference in the treated area[1]:

- Manual: 1.9” reduction on the abdomen, 2” reduction on each thigh
- Static: 2.5” reduction on the abdomen, 0.9” reduction from each thigh

Importantly, this portion of the study shed new light on the previous understanding of the treatment’s mechanism of action (i.e. how it works in the body).

The high frequency ultrasound imaging showed significant changes in the depth and density of the epidermal-dermal tissue over a course of treatments, proving clinically significant firming and toning of the skin as a key benefit.

No cryolipolysis treatment has ever reported these changes, so the clinical team investigated further.

The clinical interpretation of these changes concluded that the treatment has a direct effect on the skin structure on an epidermal-dermal level, rather than there being a lipolytic/apoptotic effect in the fat layer (hypodermis) below.

Additionally, there was no statistically significant change in BMI across the study, further reinforcing that a significant lipolysis/apoptosis is not occurring after treatment.

Armed with this new knowledge, the clinical team knew we needed to continue to pursue innovation and dive deeper into this latest clinical interpretation.

After reviewing this study, Artemis Chief Medical Officer, Dr. Sach Mohan, aided in developing and collaborating on a formal mechanism of action study to further investigate.

[1] Interestingly, the static and manual treatment data reflected different efficacy on the abdomen and thighs, which may reflect the differences in underlying epidermal/dermal structures in these areas.

SAFETY + EFFICACY STUDY

Key takeaways.

KEY TAKEAWAYS FROM THE SAFETY + EFFICACY STUDY:

- **Incredibly safe:** The study found that both the static and manual treatment modes are highly safe and unlikely to cause any significant adverse effects when used as intended.
- **Clinically-proven results:** The study found that after a course of treatments, there was clinically proven toning, tightening, and firming of the skin as well as significant circumference reduction. The average reduction in circumference after 5-10 treatments was 1.9” from the abdomen and 2” from each thigh (manual) and 2.5” from the abdomen and 0.9” from each thigh (static).
- **New knowledge:** The study shed new light on the previous understanding of the mechanism of action of the treatments based on clinical interpretation of high-frequency ultrasound doppler imaging.

Mechanism of action study

FINDINGS + INTERPRETATION

MECHANISM OF ACTION STUDY

Introduction.

- This study was designed to evaluate the temperature change of the subcutaneous fat on the abdomen following a static Shape treatment.
- Study objectives:
    - Formally rule out lipolysis/apoptosis as the mechanism of action for these treatments based on the findings of the safety + efficacy study.
    - Gain a more comprehensive understanding of how these treatments produce repeatable efficacy while maintaining such a high safety profile.
- This study was carried out using the static treatment as this treatment produces a lower temperature given its application to a highly localized area, as well as minimized risk to participants given a temperature probe was inserted subcutaneously for the duration of each treatment.

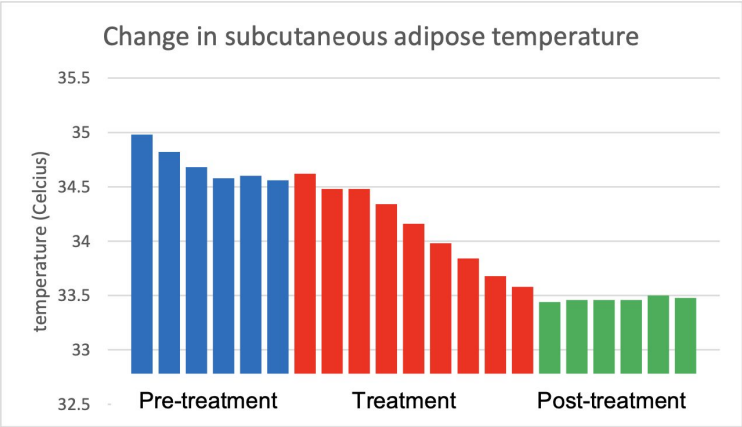
MECHANISM OF ACTION STUDY

Study design.

- This study was designed to measure the temperature change on the subcutaneous (hypodermal) fat layer following a static Shape treatment applied to the abdomen as intended.
- 5 participants completed this study. Each participant received one treatment.
- Only female participants were tested in this study. Males have higher average subcutaneous adipose deposits in the abdominal region than females, therefore the clinical team deduced that any reported subcutaneous adipose changes in males would not be elevated compared to females.
- Temperature was measured using subcutaneous thermometry guided by ultrasound imaging to verify correct placement.
- Temperature was measured for 30 minutes prior to the treatment to establish baseline, throughout the duration of the treatment, and over the subsequent 30 minutes for analysis.

MECHANISM OF ACTION STUDY

Study findings.



- While there are many studies on cryolipolysis using different protocols which make them difficult to compare, one fact is clear: cold-induced lipid crystallization (crystal-structure formation) of the adipocytes occurs at temperatures around 8°C to 10°C, and it is a condition dependent on time and temperature.[1]
- Throughout the study, subcutaneous adipose temperature varied by approximately 1 degree Celsius due to the insulating nature of subcutaneous adipose tissue.
- This finding proves that the treatments produce their clinically significant toning, tightening and firming of skin and circumference reduction through an action directly on the epidermal and dermal compartments, as shown by the stable subcutaneous temperatures recorded in this study.
- **In the safety + efficacy study, we used in vivo confocal microscopy to determine that no cellular damage (apoptosis and necrosis) occurred to epidermal cells.**
- It is not possible to determine the temperature at specific depths in the epidermis and dermis but we assume this skin layer would be cooled to close to the minimum temperature of the applied treatment as the epidermis and dermis do not have insulating fat.
- Blood flow through the skin would be continually warming the area, increasing the minimum temperature achieved.
- **The benefits of the device are therefore achieved without significant damage to the target tissues, unlike other cold temperature devices on the market.**

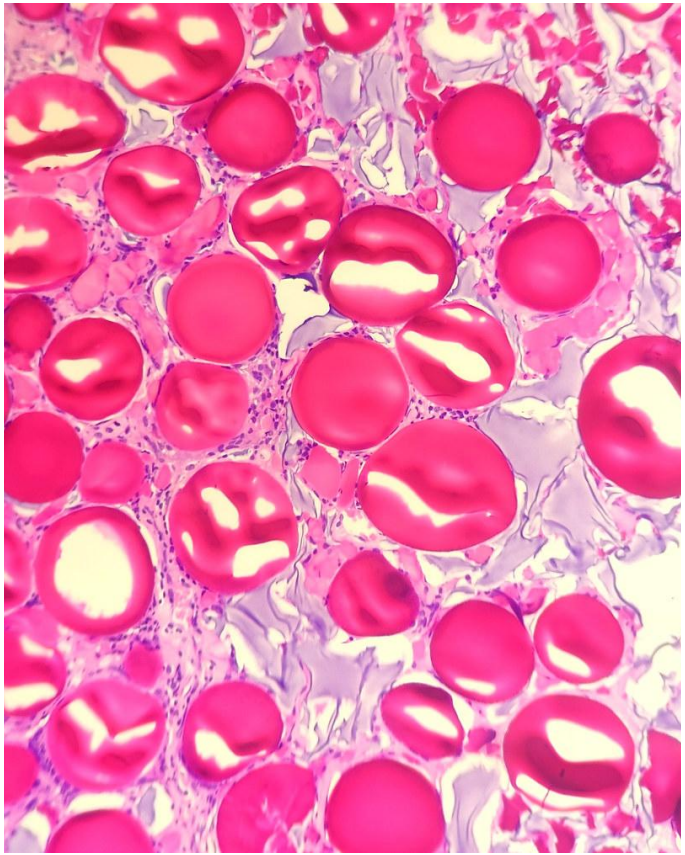
[1] *Savacini, M. B., Bueno, D. T., Molina, A. C. S., Lopes, A. C. A., Silva, C. N., Moreira, R. G., Almeida, S., Guidi, R. M., Sant'Ana, E., & Liebano, R. E. (2018). Effectiveness and Safety of Contrast Cryolipolysis for Subcutaneous-Fat Reduction. Dermatology research and practice, 2018, 5276528.* https://doi.org/10.1155/2018/5276528

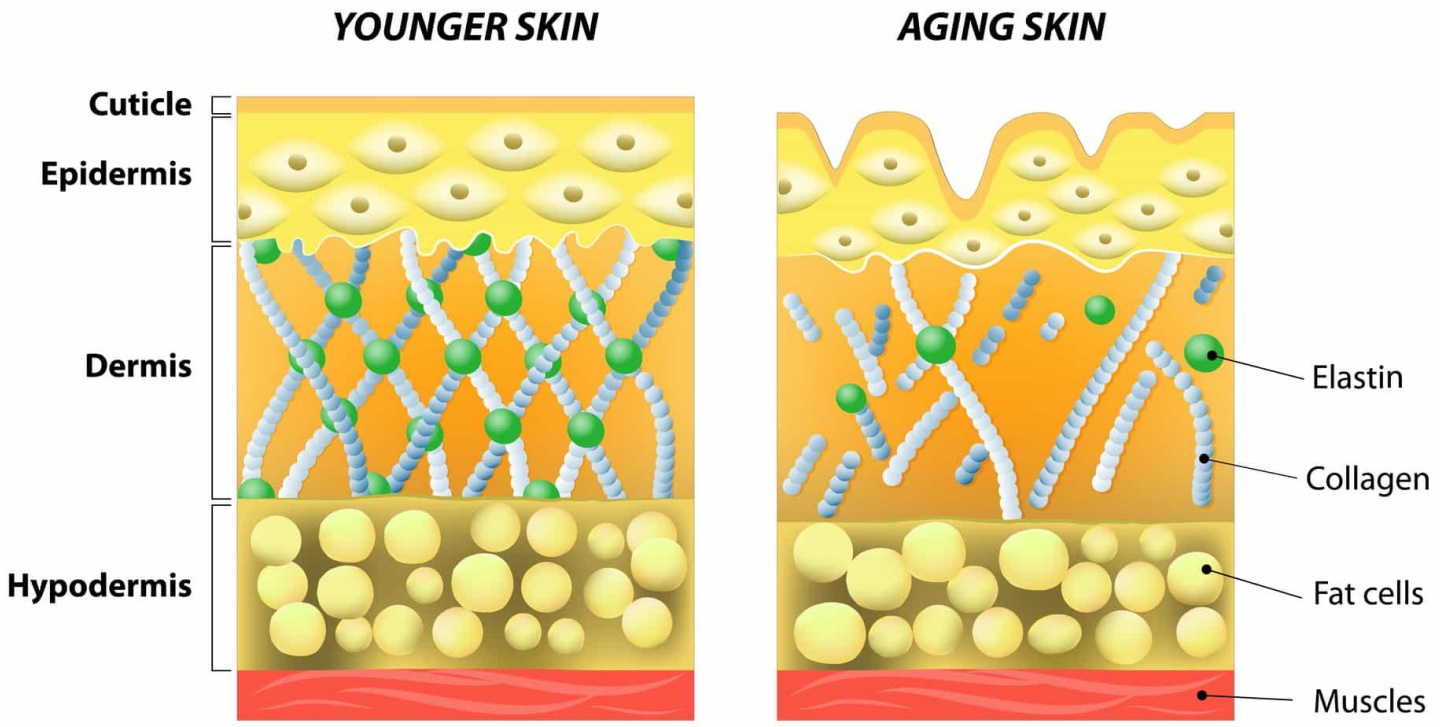

So, what is producing
these amazing results?

MECHANISM OF ACTION

Neocollagenesis.

- The results from both the safety + efficacy and mechanism of action studies have proven Shape treatments do not cause clinically significant cooling of the subcutaneous tissue and therefore achieve clinical benefits by mechanisms that do not include cellular damage (i.e. cryolipolysis, apoptosis, necrosis, etc.)
- Given these results, we can suggest that the method of action is through the activation of connective tissue in the epidermis-dermis without affecting fat cells.
- The suggested clinical hypothesis is a process known as **neocollagenesis** i.e. the stimulation of new collagen synthesis, within the dermis.
- This understanding explains the device's efficacy in achieving skin toning, tightening, firming, and circumferential reduction without inducing adverse effects associated with cellular damage.




YOUNGER SKIN
AGING SKIN
Cuticle
Epidermis
Dermis
Hypodermis
Elastin
Collagen
Fat cells
Muscles

ARTEMIS.

MECHANISM OF ACTION

What is neocollagenesis* and how does it work?

Neocollagenesis is a process in which new collagen is produced in response to inflammation and is a natural component of the body's natural wound-healing mechanism.

How and why does it happen?

Inflammation stimulates an increased production of fibroblasts and new collagen deposits, and this process of collagen remodeling leads to an increase in procollagen and matrix metalloproteinase.

Why is collagen so important?

Collagen is a vital protein in the body and a key factor in the skin's ability to become more elastic which directly affects the laxity and aging of the skin.

Clinical evidence shows that our production of new collagen starts to slow in our late 20s to early 30s. Gradually we start to lose a minimum of 1% of our collagen per year once the decline starts!

When collagen bands are strong in the dermal layer this prevents "dead space" which can present as excess circumference or a rounder appearance.

How can neocollagenesis create circumferential reduction?

Neocollagenesis aids in strengthening the extracellular matrix, which in turn creates a sustainable "collagen corset" effect. Additionally, this new production of collagen aids in improving overall skin health, firmness, and toning.

How could Shape treatments produce neocollagenesis?

The precise alternating heat and cold technology applied during Shape treatments could trigger neocollagenesis, a natural regenerative process in the body, producing clinically-proven circumferential reduction and skin toning, tightening, and firming.

How long does the new collagen last once formed?

Once new collagen is formed, it has a lifespan of 6 years. However, this doesn't stop time (i.e. reabsorption caused by age, genetic predisposition, lifestyle, etc) and therefore ongoing maintenance is recommended.

Where were the changes observed in the skin within the clinical study results?

Given the epidermis (the skin layer seen by the naked eye) is a series of morphologically distinct dead layers of skin, all of the structural changes that were observed and analyzed throughout the studies ultrasound were on the capillary and reticular dermis.

The compaction of this layer demonstrates that the Shape treatments produce a better organization of the structures that comprise it, including the collagen matrix to form the scaffolding to the skin.

This increased density is responsible for the circumferential changes that were clinically-proven by the safety + efficacy study.

Please note: Neocollagenesis is the working clinical hypothesis of the mechanism of action based on our Chief Medical Advisor's review of our clinical studies.

Key highlights + takeaways

ARTEMIS.

KEY HIGHLIGHTS + TAKEAWAYS

Key highlights + takeaways.

Incredibly safe

The study found that both the static and manual treatment modes are highly safe and unlikely to cause any significant adverse effects when used as intended.

Exceptionally effective

The study found that after a course of treatments, there was clinically proven toning, tightening, and firming of the skin as well as significant circumference reduction. The average reduction in circumference was 1.9” from the abdomen and 2” from each thigh (manual) and 2.5” from the abdomen and 0.9” from each thigh (static).

Pushing innovation

The MOA study is the only human paper of its kind - the only previous studies on this topic have been completed with swine!

New understanding of mechanism of action (MOA)

This new understanding is an absolute game-changer for so many reasons:

- Not only is our new understanding of MOA even *less* invasive, it also is a key part of maintaining overall skin health and wellness.
- This MOA doesn’t impact efficacy, as we have clinically proven these treatments deliver world-class results to motivate clients on their beauty + wellness journeys.
- This new understanding of MOA allows practitioners to position these treatments as the perfect complement to to any weight loss program as it (a) motivates people by giving them a fairly quick inch loss and (b) tightens up loose skin (within parameters) caused by weight loss.

Competitive advantage

Same efficacy, new understanding. No surgery, no downtime, just incredible results in under an hour.

Based on our MOA temperature study, we can also deduce that Shape would not lead to serious adverse events (such as PAH) seen with other cold temperature devices as the subcutaneous fat layer does not cool to the temperatures required, nor have a mechanized suction component, thus there is not the same risk of tissue damage or trauma.[1]

Strong argument for state boards

We now have an even stronger argument, with robust clinical evidence to back it up, when asking state boards to review the position of esthetician usage of the device as it does NOT damage any living tissue, is clearly not a cryosurgical device, cryolipolysis, etc.

1 *A Multicenter Evaluation of Paradoxical Adipose Hyperplasia Following Cryolipolysis for Fat Reduction and Body Contouring: A Review of 8658 Cycles in 2114 Patients* & *Paradoxical Adipose Hyperplasia and Cellular Effects After Cryolipolysis: A Case Re*

ACKNOWLEDGEMENTS

Study credits

CRO:

- CUTEST Systems LTD

PRINCIPAL INVESTIGATOR:

- Stewart Long, BSc

CO-INVESTIGATOR & DERMATOLOGIST CLINIC PERSONNEL:

- Dr Richard Goodwin, MBBS, MRCP
- Ms T Davies RGN
- Ms H Evans-Hunte RGN
- Mrs L McLundie RGN
- Ms T Welsby BSc
- Ms L Miles BSc
- Mr J Davies MSci
- Ms A Corcoran MSc
- Mr C O'Brien MSci
- Mr A Beynon BSc
- Ms P Ward MSc

Thank you!

ARTEMIS.