Cover Letter:

Enclosed bellow documents are part of the Clinical Trial NCT03769649

Study Name: **Clinical Evaluation of Safety and Efficacy of The CelluTite Treatment**

Revision Date: August 15, 2019

Study Name: **Clinical Evaluation of Safety and Efficacy of The CelluTite Treatment**

Protocol No.: DO608110

Revision No.: 4

Sponsor: **InMode MD Ltd.**

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1. Protocol Synopsis

Study Title	Evaluation of Safety and Efficacy of The CelluTite Treatment
Protocol No	DO608110C
Sponsor	InMode MD Ltd.
Device	InMode RF system CelluTite RFAL hand piece HP172248. Morpheus8 Applicator
Study Design	Prospective single centre, open label clinical study.
Study Objectives	The aim of the study is to evaluate the safety and efficacy of cellulite treatment with HP172248 and Morpheus8.
Study Sites	Dr. Bruce Katz, 60 E 56th St #2, New York, NY 10022, USA
Patient Population and Sample Size	Approximately 10 female subjects , aged 18-70 having grade II and mild/moderate grade III cellulites.
Treatment areas	Exterior (lateral) and posterior thighs Optional: Buttocks with Morpheus Applicator only
Study Duration	Study duration for each subject is approximately seven months (including screening, one treatment and four follow-up visits at 1 week, 1 month, 3 months and 6 months post treatment. Overall study duration will be approximately 12 months, depending on the subject recruitment rate.
Efficacy Endpoints	Photographs evaluation: Photos from all time points (baseline and follow-up visits) will be evaluated by the treating physician and 2 blinded independent evaluators. Optional: Photos will be taken using QuantifiCare (imaging specializing in skin evaluations in clinical trials) at baseline and 6M FU visit. Evaluation goals are rating the degree of cellulite according to Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS).

Safety Endpoint	Observation, assessment and recording of adverse events. Evaluations will be done immediately after treatments and at all follow-up visit. The frequency, severity and causality of all adverse events will be recorded. Possible treatment adverse effects include but are not limited by: - Discomfort or pain - Excessive skin redness (erythema) - Excessive skin swelling (edema) - Bruising - Damage to natural skin texture (crust, blister, burn) - Change of pigmentation (hyper- and hypo-pigmentation) - Scarring - Excessive Bleeding - Surface Irregularity - Numbness - Seroma - Severe and persistent reactions are reportable as adverse events.
	Each subject will undergo at least 5 study visits including screening, 1 treatment and 4 follow-up visits. **Visit 1**: - Screening will be performed to determine subject eligibility as well as to collect all of the required medical information and obtain signed Informed Consent. - Baseline photos will be performed. - Treatment may occur on the same day of screening or within 3 weeks following screening. **Visit 2:** Follow-up visit – 1 week following treatment. Safety follow-up to insure that patient recovery is proper. Photos and assessments will be performed. **Visit 3:** Follow-up visit – 1 month following treatment. Photos and assessments will be performed. **Visit 4:** Follow-up visit – 3 months following treatment. Photos and assessments will be performed. **Visit 5:** Follow-up visit – 6 months following treatment. Photos and assessments will be performed. - After the treatment and at all visits, adverse events will be recorded. - Duration of the screening and treatment visit is approximatly 2-3 hours and the follow-up visit is approximatly 1 hour.
Main Eligibility Criteria	<u>Inclusion Criteria</u> - Female subjects aged 18-70 having mild/moderate grade cellulites.

	- The patients should understand the information provided about the treatment, possible benefits and side effects, and sign the Informed Consent Form, (including the permission to use photography). - The patients should be willing to comply with the study procedure and schedule, including the follow up visit, and will refrain from using any other aesthetic treatment methods in the treatment area for the last 6 months and during the entire study period. <u>Exclusion Criteria:</u> - Body fat layer thinner than 5mm. - Pacemaker or internal defibrillator, or any other active electrical implant anywhere in the body. - Superficial permanent implant in the treated area such as metal plates and screws, metal piercing, silicone implants or an injected chemical substance. - Current or history of skin cancer (remission of 5 years), or current condition of any other type of cancer, or pre-malignant moles. - Severe concurrent conditions, such as cardiac disorders, epilepsy, uncontrolled hypertension, and liver or kidney diseases. - Pregnancy and nursing. - History of bleeding coagulopathies or use of anticoagulants. - Impaired immune system due to immunosuppressive diseases such as AIDS and HIV or use of immunosuppressive medications. - Poorly controlled endocrine disorders, such as diabetes or thyroid dysfunction and hormonal virilization. - Any active condition in the treatment area, such as sores, psoriasis, eczema, and rash. - History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin. - Use of Isotretinoin (Accutane®) within 6 months prior to treatment. - Any surgery or treatment such as laser or chemicals in treated area within 3-6 months prior to treatment or before complete healing. - Allergies, in particular to anesthesia. - Mental disorders such as Body Dysmorphic Disorder (BDD). - As per the practitioner's discretion, refrain from treating any condition that might make it unsafe for the patient.

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2. Introduction & Study Rationale

Cellulite affects 85–98% of post-pubertal females of all races. While not a pathologic condition, it remains an issue of cosmetic concern to a great number of individuals. Cellulite describes the orange peel or cottage cheese-type dimpling of skin seen most commonly on the thighs and buttocks. It is prevalent in women of all races but is more common in Caucasian females. Cellulite can be located in any area of the body that contains subcutaneous adipose tissue Although cellulite may be found in any area where excess adipose tissue is deposited, obesity is not necessary for its presence.
The desire for minimally invasive safe and less traumatic cellulite treatments has grown substantially in recent years. Minimally invasive, temperature-controlled radiofrequency (RF)-based technology offers an optimal energy-based alternative.
Radiofrequency-assisted lipolysis (RFAL) technology was introduced by InMode Ltd., Israel about 10 years ago. RF energy is applied to the treatment area using a handpiece with 2 electrodes. An internal active electrode emitting coagulative thermal energy targets the deep soft tissues, as well as releases tissue in dimples by cutting fibrous septa with spatula-shaped tip.
The external electrode is larger compared to the internal electrode, thus having relatively low energy density that creates nonablative RF heating. RF flows between the internal and the external electrode placed on the skin, heating the tissue in between the electrodes and causing a thermo coagulative effect. The treatment stimulates contraction and collagen formation and simultaneously coagulates and liquifies adipose tissue with profound contraction of the fibro-septal network (FSN)[1-4]. The RFAL technology became a well-established alternative for body[3,4], face and neck[2,5-7] rejuvenation treatments using RFAL based handpieces.
InMode RF technology with a few handpieces was cleared by the FDA for electro-coagulation and hemostasis (K171593, K163190, K151793).

The InMode system with the Morpheus8 Handpiece (K180189) is designed for delivering RF energy to the skin surface in a fractional manner. The energy is delivered to the skin through bipolar arrays of 24 insulated pins and results in localized heating and ablation of the skin that is in direct contact with the pins non-insulated tip. Ablation of the skin promotes skin renewal while untreated skin between the pins enables faster healing of the tissue. There is also the contribution of non-ablative, non-coagulating dermal matrix heating that occurs in the skin that is not subject to fractional ablation.

This prospective study is intended to evaluate the safety and efficacy of a new CelluTite RFAL handpiece combined with Morpheus8 handpiece for the treatment of cellulite.

3. Definitions, Acronyms and Abbreviations

RF - Radiofrequency

RFAL - Radiofrequency-assisted lipolysis
AE - Adverse Events
SAEs - Serious Adverse Events
UADEs - Unanticipated Adverse Device Effects
HP - Handpiece

4. Device Description

The InMode RF™ System is employing radiofrequency (RF) energy for use in dermatological and general surgical procedures for electrocoagulation and hemostasis. The System operates when Handpiece is connected.
The InModeRF System with CelluTite HP provides individual adjustment of treatment parameters to achieve maximum efficiency and safety for the specific treatment.
The System provides enhanced safety while minimizing possible side effects by monitoring RF parameters and tissue temperature.

The System incorporates the following safety features. All personnel operating the System should be familiar with these features.

- System has unique password to avoid device operation by non-authorized personnel.
- The RF energy cannot be activated unless the applicator and footswitch have been connected to the System.
- An audible tone indicates energy activation.
- During activation, the System performs a self-test of the hardware.
- Hardware is tested every 10ms to ensure proper operation of electrical circuit.
- Tissue impedance monitoring prevents accidental energy emission to the patient.
- Skin surface is monitored during the treatment. RF energy delivery is terminated when skin temperature accidentally reaches the Cut-off level.
- System starts at a low setting.
- Internal and skin surface temperature and impedance are constantly monitored.

The InMode System with the Morpheus8 HP is designed to deliver radiofrequency energy to the skin in a non-homogeneous fractional manner, via an array of 24-electrode pins. The array delivers bipolar RF energy to the skin, resulting in heating of skin around the electrodes contact, to temperatures leading to electrocoagulation and homeostasis of small portions of the skin. The procedure is carried out while leaving untouched areas in-between the pin electrodes. This

maintains the integrity of the treated skin and serves as a reservoir of cells that accelerate and promote the healing process.

The System provides individual adjustment of treatment parameters to achieve maximum efficiency and safety for each patient and applications.
The Morpheus8 HP contains the following safety features:

- System has a password to avoid device operation by non-authorized personnel.
- The power electronics cannot be activated unless the applicator and footswitch have been connected to the System.
- An audible tone indicates energy activation.
- During activation, the system performs a self-test of the hardware.
- Hardware is tested every 10ms to ensure proper operation of electrical circuit.
- System starts at a low setting.

5. Study Objectives

The objective of this clinical study is to evaluate the safety and efficacy of treatment with CelluTite RFAL HP and Morpheus8 HP.

6. Study Endpoints

6.1 Efficacy Endpoints

Photographs evaluation: Photographs should always be taken under the same settings, including distance, angle, background, lighting and body position. Angles to include front, back and side views (90º angles and 30º angles).

Photos from all time points (baseline before treatment and at follow-up visits) will be evaluated by the treating physician and 2 independent evaluators.

Optional: Photos will be taken using QuantifiCare (imaging specializing in skin evaluations in clinical trials) at baseline and 6M FU visit

Clinician Reported Photonumeric Cellulite Severity Scale (CR-PCSS)[8]: This 5-point photonumeric scale rates cellulite severity from "0" (none) to "4" (severe) from a clinician's perspective in two main clinical morphologic features of cellulite (categories): (A) number of evident dimples (Figure 1); and (B) severity of linear undulations (contour irregularities) (Figure 2).

Table 1. Cellulite Severity Scale

	0	1	2	3	4
Number of evident dimples	(A) None/no dimples	(B) 1 dimple	(C)2 dimples	(D) 3 dimples	(E) 4 or more dimples
Severity of linear undulations (contour irregularities)	(A) None—no depressions or raised areas	(B) superficial: generalized, small depressions with no protuberances;	(C) mild: pattern of mild linear undulations with alternating areas of protuberances and depressions	(D) moderate: pattern of moderate linear undulations with alternating areas of protuberances and depressions	(E) severe: severe generalized linear undulations with alternating areas of protuberances and depressions

Figure 1. Number of evident dimples

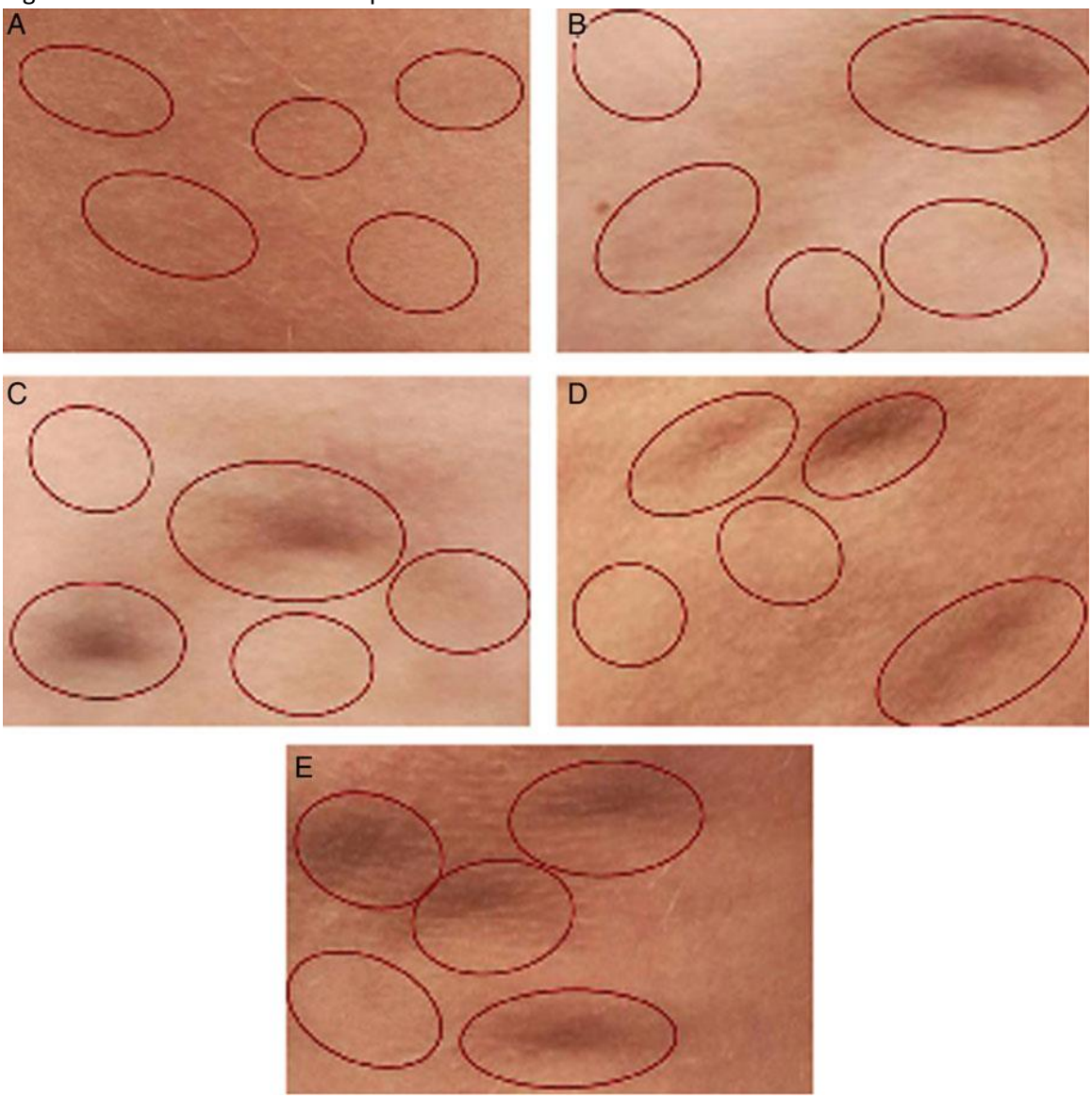
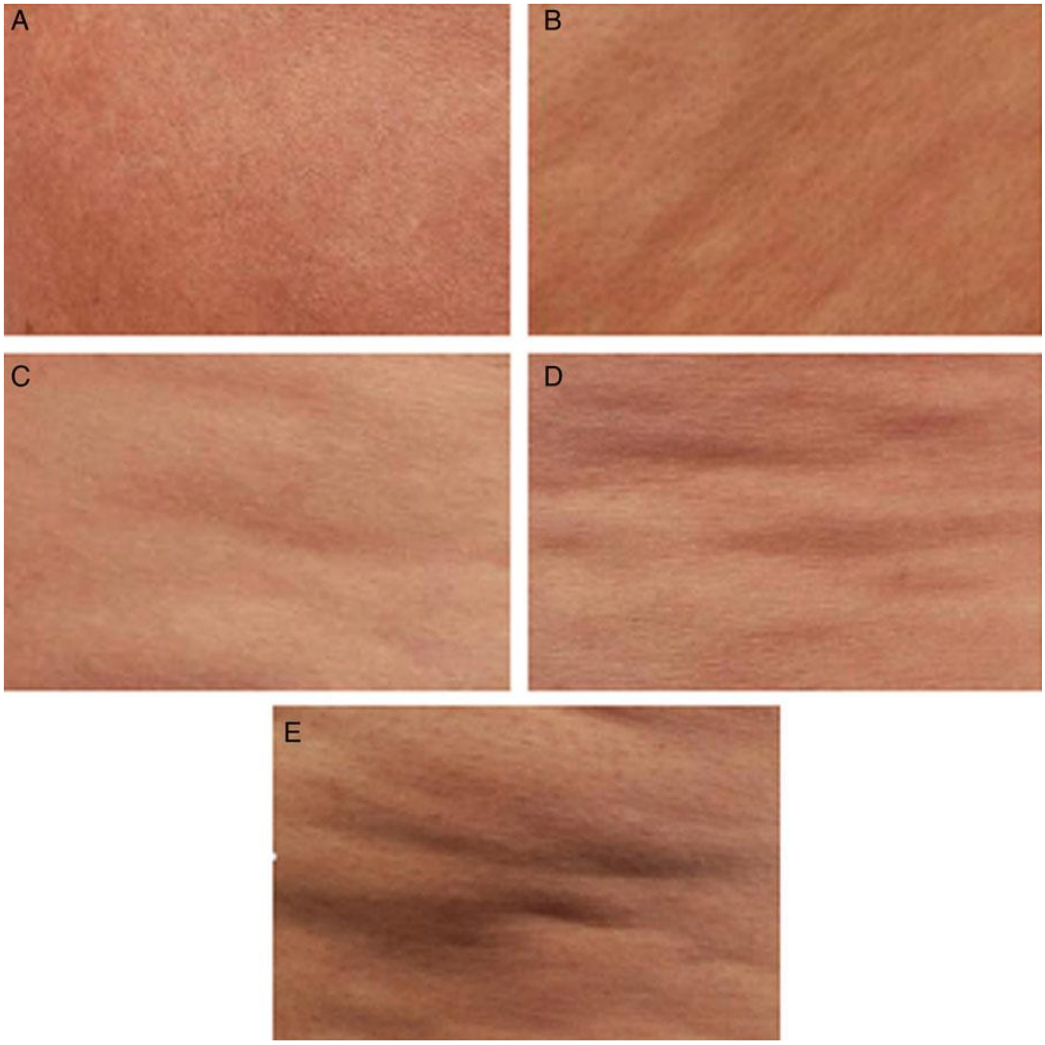


Figure 2. Severity of linear undulations (contour irregularities)



6.2 Safety Endpoint

Observation, assessment and recording of adverse events. Evaluations will be done immediately after treatment and at all follow-up visits. The frequency, severity and causality of all adverse events will be recorded.

Possible CelluTite adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)

- Excessive skin swelling (edema)
- Ecchymosis
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Scarring
- Very slight risk of infection
- Incision port scarring
- Surface Irregularity
- Numbness
- Seroma
- Side effects related to anesthesia

Possible Morpheus8 adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Localized infection
- Scarring

Erythema lasting not longer than 24h and edema for 1-3 weeks is a typical skin reaction to the Morpheus8 treatment.

Crusting from the ablated dots will exfoliate naturally after 1-3 weeks.

Adverse events will be classified as Mild, Moderate, and Severe.
The duration of the adverse event until it subsides will also be recorded.

7. Study Population

7.1 General Considerations

The study will recruit approximately 70 female subjects, between the ages of 18-70, having small body areas with adipose tissue, seeking cellulite treatments.

Treatment areas include Exterior (Lateral) and posterior thighs

Optional: Buttocks treated with Morpheus Applicator only

Eligible subjects will be screened. Investigators will screen subjects based on the inclusion/exclusion criteria described below after a written informed consent is signed.

7.2 Inclusion Criteria

- Female subjects aged 18-70 having mild/moderate grade cellulites.
- The patients should understand the information provided about the treatment, possible benefits and side effects, and sign the Informed Consent Form, (including the permission to use photography).
- The patients should be willing to comply with the study procedure and schedule, including the follow up visit, and will refrain from using any other aesthetic treatment methods in the treatment area for the last 6 months and during the entire study period.

7.3 Exclusion criteria

- Body fat layer thinner than 5mm.
- Pacemaker or internal defibrillator, or any other active electrical implant anywhere in the body.
- Superficial permanent implant in the treated area such as metal plates and screws, metal piercing, silicone implants or an injected chemical substance.
- Current or history of skin cancer (remission of 5 years), or current condition of any other type of cancer, or pre-malignant moles.
- Severe concurrent conditions, such as cardiac disorders, epilepsy, uncontrolled hypertension, and liver or kidney diseases.
- Pregnancy and nursing.
- History of bleeding coagulopathies or use of anticoagulants.
- Impaired immune system due to immunosuppressive diseases such as AIDS and HIV or use of immunosuppressive medications.
- Poorly controlled endocrine disorders, such as diabetes or thyroid dysfunction and hormonal virilization.
- Any active condition in the treatment area, such as sores, psoriasis, eczema, and rash.
- History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin.
- Use of Isotretinoin (Accutane®) within 6 months prior to treatment.
- Any surgery or treatment such as laser or chemicals in treated area within 3-6 months prior to treatment or before complete healing.
- Allergies, in particular to anesthesia.
- Mental disorders such as Body Dysmorphic Disorder (BDD).
- As per the practitioner's discretion, refrain from treating any condition that might make it unsafe for the patient.

8. Study Design

The study is a prospective, open label clinical study.
Approximately 70 subjects will be recruited for the study.

Treatment areas include Exterior (Lateral) and posterior thighs

Optional: Buttocks treated with Morpheus Applicator only

The treatment will be conducted according to the guidelines in the operator manual.

The treatment efficacy will be evaluated by comparing 1, 3 and 6 months follow-up photos and cellulite grade to baseline.

Each subject will undergo 5-6 study visits including screening, treatment and 4 follow-up visits.

The Time and Events Schedule is provided in Appendix I.

8.1 Screening and Baseline (Visit 1)

Screening visit will be performed in order to determine subject eligibility and to collect all required demographic and baseline clinical information. Study procedures and available treatment options, including the CelluTite RFAL and Fractional RF technology will be described in detail to the subject. Subject will be assured that the decision regarding participation in the study is strictly voluntary and that they are free to change their mind at any stage. Subjects who decide to participate in the study will sign the Informed Consent form and Photo Release form prior to any study related procedure.

Subjects will then be screened for study eligibility according to inclusion and exclusion criteria.

The following Demographic and Baseline Measurements will be performed:

- Demographic data including gender, age, race, skin type (Fitzpatrick scale).
- Medical history and concomitant medication usage.
- Baseline photos and assessments will be taken.

8.2 Treatment

The CelluTite HP treatment may occur on the same day of screening and baseline visit (or within 3 weeks following screening).

Treatment area: Treatment areas include exterior (lateral) and posterior thighs Optional: Buttocks treated with Morpheus Applicator only

Treatment procedure

- Treatment will be conducted according to instructions in the operator manual and company guidelines.

- Local anesthesia should be injected, incisions should be created for tumescent and internal electrode insertion and tumescent anesthesia should be applied. Make two or three incisions for each side. One on the low side of the thigh and 1 or 2 on the top area.
- Sterile water–based gel, such as ultrasound gel should be applied to the skin surface to insure good contact of external electrode.
- Insert CelluTite cannula to the most distal protrusion.
- Treat protrusion area to reach internal cut off. Treat depressed areas without energy to mechanically release septa and elevate the dimples.
- Treat only in one plane at the depth of 7-20mm depending on fat thickness and severity of cellulite.
- Use 40°C external cut-off and 60°C internal cut-off. Higher setting (40°C/70°C) can be used for depth 15-20mm.
- Cannula should be inserted to the intended tissue and good contact of return electrode with skin surface should be ensured.
- While RF is applied, footswitch should be pressed.
- Treat all dimples/depressions in the treatment area.
- Treat all marked areas uniformly.
- After RFAL heating, no or minimal aspiration is recommended. Aspiration is performed with slow cannula movement to take liquified fat out without additional mechanical destruction of tissue. However, aggressive external “milking” of melted fat out of the treatment zone should be performed through the incision port to reduce risk of seroma and level of inflammation. Even pressure should be applied when milking the treatment area to achieve outcomes that are uniform in contour.
- Endpoint of the CelluTite treatment is achievement of temperature cut-off.
- Set Morpheus8 hand piece with BODY treatment depth and energy level of 40 in Fixed mode and double stack with 2 consecutive pulses on the same spot. Apply 2 passes of Morpheus8 with 50% overlap to all treated area.

If subject has grade III cellulite and dimples are present:

.1 Step 1: Release bands/dimples with the CelluTite handpiece exercising caution not to reach maximum cutoff temperature.
- Step 2: Set Morpheus8 hand piece with BODY treatment depth and energy level of 40 in Fixed mode and double stack with 2 consecutive pulses on the same spot. Apply 2 passes of Morpheus8 with 50% overlap to all treated area.Step 3: Harvest Fat and Fat Transfer - additional procedure called fat grafting and/or EVL (Expansion Vibration Lipofilling) might be performed to further expand and even the area of concern. During this procedure the physician will remove unwanted fat from a "donor" zone and add it to another zone of the thigh. If subjects meet the criteria for this procedure it will be discussed during the screening.
- Loose closing of the incision port with a suture provides drainage of treated area after the treatment.
- Compressing garments must be applied at least for 1-2 weeks following the treatment.

- Optional: Apply topical anesthesia on Buttocks area and treat with Morpheus Applicator only. Set Morpheus8 hand piece with BODY treatment depth and energy level of 40 in Fixed mode and double stack with 2 consecutive pulses on the same spot. Apply 2 passes of Morpheus8 with 50% overlap to all treated area.

After treatment, observation, assessment and recording of adverse events will be conducted.

8.3 Follow up visits (Visits 2-5)

Four follow up visits will be conducted and 1 week, 1Month, 3 Months and 6 months post last treatment.

The follow up visits will include the following assessments:

- Camera photos
- Cellulite evaluation
- AE evaluation recording
- Concomitant medication recording

9. Efficacy and Safety Evaluations

9.1 Efficacy Measures

The below assessments will be conducted at baseline and follow-up visits.

Photos from all time points (baseline before treatment and at follow-up visits) will be evaluated by the treating physician and 2 blinded independent evaluators.

Evaluation goals are rating the degree of cellulite.

9.2 Safety Measures

Observation, assessment and recording of adverse events. Evaluations will be done immediately after treatment and at all follow-up visits, to determine if adverse events develop or persist. The frequency, severity and causality of all adverse events will be recorded.

Possible CelluTite adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Ecchymosis
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Scarring

- Very slight risk of infection
- Incision port scarring
- Surface Irregularity
- Numbness
- Seroma
- Side effects related to anesthesia

Possible Morpheus8 adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Localized infection
- Scarring

Erythema lasting not longer than 24h and edema for 1-3 weeks is a typical skin reaction to the Morpheus8 treatment.

Crusting from the ablated dots will exfoliate naturally after 1-3 weeks.

Adverse events will be classified as Mild, Moderate, and Severe.
The duration of the adverse event until it subsides will also be recorded.

10. Subject Compliance

10.1 Subject Discontinuation or Withdrawal

Subjects will be suspended temporarily or terminated from the study whenever considered necessary for their welfare.

The investigator may withdraw a subject if, in his judgment, it is in the best interest of the subject, if the subject cannot comply with the protocol, or if a Serious Adverse Event occurred.

Each subject must complete the 6 months follow-up visit in order to remain in the study.

If a subject withdraws, the reason must be recorded in the CRF Exit Form and signed by the Investigator.

10.2 Compensation for Study Participation

There is no cost to subject for participation and any potential stipend will be clearly explained in the ICF.

11. Risk / Benefit Analysis

11.1 Potential Risks

Risk is the product of the likelihood that an adverse medical event will occur times the severity of the event. The main potential risks of using the CelluTite an Morpheus8 handpieces are specified below.

Possible CelluTite adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Ecchymosis
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Scarring
- Very slight risk of infection
- Incision port scarring
- Side effects related to anesthesia
- Surface Irregularity
- Numbness
- Seroma

Possible Morpheus8 adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Localized infection
- Scarring

Erythema lasting not longer than 24h and edema for 1-3 weeks is a typical skin reaction to the Morpheus8 treatment.

Crusting from the ablated dots will exfoliate naturally after 1-3 weeks.

11.2 Benefits

Subjects may experience cellulite improvement. Each individual may get different level of clinical aesthetic results.

12. Adverse Events Reporting

12.1 Definitions

Adverse Event:

An Adverse Event (AE) is any untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) in a subject. This definition does not imply that there is a relationship between the adverse event and the device. (Significant device failure may constitute an adverse event if an undesirable experience occurs).

An Adverse Device Effect (ADE) is any untoward and unanticipated response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device, or any event that is a result of a user error.

Serious Adverse Event (SAE):

A serious adverse event (SAE) is any adverse event that:

- Led to death
- Led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury
- Resulted in a permanent impairment of a body structure or a body function
- Required in-subject hospitalization or prolongation of existing hospitalization
- Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Led to fatal distress, a congenital abnormality, birth defect or death

Unanticipated Adverse Event:

An unanticipated adverse event is any serious, device-related adverse event, if that event was not previously identified in the risk analysis and Informed Consent form in nature, severity, or frequency.

AE Severity:

Adverse events are graded according to severity as follows:

Mild	Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
Moderate	Sign or symptom, which may be ameliorated by simple therapeutic measures; yet, may interfere with usual activity.
Severe	Sign or symptom that are intense or debilitating and that interfere with usual activities. Recovery is usually aided by therapeutic measures.

Relationship to Device:

The relationship of the adverse event to the treatments or procedures is defined as follows:

Most Probably Related	Follows a reasonable temporal sequence from study device delivery/retrieval and cannot be reasonably explained by known

	characteristics of the subject's clinical data or the surgical procedure applied.
Possibly Related:	Follows a reasonable temporal sequence from study device delivery/retrieval but could have been produced by the subject's clinical state or by the surgical procedures regardless of the study device.
Probably not Related:	Temporal association is such that the study device is not likely to have had any reasonable association with the observed event.
Unrelated	No relationship to study device activation is perceived

12.2 Anticipated Adverse Events in this Clinical Evaluation

Possible CelluTite adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Ecchymosis
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Scarring
- Very slight risk of infection
- Incision port scarring
- Side effects related to anesthesia
- Surface Irregularity
- Numbness
- Seroma

Possible Morpheus8 adverse effects include but are not limited by:

- Discomfort or pain
- Excessive skin redness (erythema)
- Excessive skin swelling (edema)
- Damage to natural skin texture (crust, blister, burn)
- Change of pigmentation (hyper- and hypo-pigmentation)
- Localized infection
- Scarring

Erythema lasting not longer than 24h and edema for 1-3 weeks is a typical skin reaction to the Morpheus8 treatment.

Crusting from the ablated dots will exfoliate naturally after 1-3 weeks.

12.3 Precautions to Minimize Complications

A list of warning and precautions is provided in the Operator Manual which is provided to site personnel.
Additionally, the exclusion criteria listed in this protocol further reduce the abovementioned risks.

12.4 Investigator Records

The Investigator will report all Adverse Events which occur with each subject throughout the study and follow-up period and will record them in the CRF Adverse Events Investigation Form. The Investigator will categorize Adverse Events according to:

- Serious or non-serious
- Severity
- Anticipated or unanticipated
- Relationship to device use

12.5 Investigator Reporting of AEs

The Investigator will report all serious adverse events (SAEs) to InMode MD Ltd by telephone as soon as becoming aware of them. A written follow-up report will be emailed or faxed to InMode MD Ltd and the reviewing IRB within 24 hours and will include the following information:

1. Nature of AE
2. Statement regarding the degree to which it is considered device related, and rationale.
3. Results of any diagnostic tests that were performed.
4. Description of any treatment implemented.
5. Statement of subject's current clinical status.
6. Investigator's signature and date.

Non-serious adverse events that are unanticipated and may be device related will be reported to the InMode MD Ltd by telephone within 24 hours. A written follow-up written report will be emailed or faxed to InMode MD Ltd within 5 working days and will include the following information:

1. Nature of adverse effect.
2. Statement as to why it is considered unanticipated.
3. Statement as to the degree to which it is considered device related, and rationale.
4. Results of any diagnostic tests that were performed.
5. Description of any treatment implemented.
6. Statement of subject's current clinical status.
7. Investigator's signature and date.

All other Adverse Events will be reported in writing to InMode MD Ltd in writing within 5 working days of the Investigator becoming aware of them.
The Investigator will continue to clinically monitor the AE, with laboratory tests where appropriate, until it is resolved, stabilized or there is a return to baseline.

13. Regulatory Aspects

13.1 Institutional Review Board

The study protocol, informed Consent forms (all versions), and any specific advertising will be submitted to and approved by Sterling Institutional Review Board (IRB), at 6300 Powers Ferry Road · Suite 600-351, Atlanta, Georgia 30339, Toll-Free: (888) 636-1062, Phone: 770-690-9491, Fax: (770) 690-9492 before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification will be provided to the sponsor.

13.2 Protocol

Protocols will be noted as approved by the Investigator by placement of his signature on the Investigator's Signature Page. The protocol and Informed Consents will be provided, and the site shall assure IRB approval prior to any study related activities.

13.3 Informed Consent

An Informed Consent that includes all of the relevant elements currently required by FDA or state regulations will be provided to each prospective study patient at screening and before enrolling into the study. The type and method of study, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator of designee. Once the Investigator is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give Consent by signing and dating in the appropriate areas of the Informed Consent form. The Investigator or Designee will also sign and date the form. A copy of the IRB approved IC form will also be provided to InMode MD Ltd.

13.4 Protocol and Informed Consent Changes

Changes to the protocol or Informed Consent Form will be implemented as amendments to the original document and approved by the IRB. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and IC amendments/revisions, along with letters noting IRB approval, will be submitted to InMode MD Ltd, as this may affect safety. Any addenda, amendment or revision that substantially alters the study design or increases potential risk to the patient requires the patient's Consent to continue in the study.

13.5 Product Accountability

All device and related materials receipt, inventory, dispensing, and reconciliation records will be maintained in compliance with Federal Regulations. Upon completion or termination of the study the site will be responsible for retaining all partial and unused products under FDA regulations.

13.6 Privacy of Personal Data

The subject's name and personal data will remain confidential and will not be published in any way. All reports and communications relating to study subjects will identify the subject only by his/her case number and study 3-letter code. The Study staff will complete subject identification in a confidential enrolment log, which will be used for the purposes of traceability and follow-up. This will be treated with strict adherence to professional standards of confidentiality and will be filed under adequate security and restricted accessibility

14. Documentation

14.1 Documentation List

Accurate, complete and timely documentation is essential to the successful conduct of this study. The following documents will be created and maintained:

1. Informed Consent Forms (ICFs).
2. Case Report Forms (CRFs).
3. Adverse effect reports to sponsor.
4. Adverse effect reports to IRB.
5. Inventory Log.
6. Monitoring logs.
7. IRB approval for protocol.
8. IRB approval for informed Consent.
9. Final report to Sponsor and IRB.
10. Records of protocol deviations.
11. Record of protocol amendments.
12. 1 copy of each protocol revisions.
13. 1 copy of each CRF revision.
14. Clinical Trial Agreement.
15. All correspondence relating to study.

14.2 Case Report Forms (CRFs)

CRFs will be designed for recording the required demographic and clinical information and the variables to be analysed, as described by this protocol.

CRFs will be completed by the authorized Investigator or a designee who will be properly trained on study procedures and data recording requirements. Upon completion, the CRFs will be signed by the Principal Investigator.
CRFs will be provided by the sponsor, one CRF per subject, each one numbered.
Study data will be recorded directly onto the CRF as soon as it is collected. The following data will be recorded pre-procedure, during the procedure, and post-procedure on the CRFs:

1. Baseline Data Form – to be used for screening subjects for inclusion in the study and to record subject's demographic data and medical history.
2. Training Form – to be used for recording relevant training information.
3. Treatment Visit Forms – to be used to record procedural details, procedural complications, technical performance of the device, test results and other relevant information related to the procedure and device.
4. Unscheduled Visit Form – to be used to record procedural details, procedural complications, technical performance of the device, and other relevant information related to the procedure and device during an unscheduled visit to site.
5. Termination Form - to be used to record all details regarding the termination of the subject, whether a result of study completion or premature withdrawal.
6. Exit Form – To be completed after all study procedures, follow-up and completion of AE investigation for the subject.
7. Adverse Event Investigation Form – to be used to report all AE, if occurred.

14.3 Protocol Modifications

An amendment to the protocol may be proposed by an Investigator or the Sponsor. The amendment will be prepared and approved by the Sponsor according to the Sponsor's Procedure. Significant amendment will be submitted to the IRB for approval before implementation.
If for any unexpected reason it is necessary to deviate from the procedures stated above, the protocol deviation should be discussed with the Sponsor representative. It must be approved by the Investigator and Sponsor representative. The deviation and reasons for it will be described in the appropriate Protocol Deviation Form, signed and filed in the relevant section of the Sponsor Study File following approval.
A copy of the document must be filed in the Investigator Study File.
Any deviation must be noted in the Study Report. If a deviation has any implication of impact on the study objectives it must also be included in the summary.

14.4 Maintenance and Retention of Records

Investigators will maintain all study related documentation for a period of two years following: 1) marketing authorization for device commercialization, or 2) sponsor's withdrawal of submission for approval, or 3) completion of the study.

All printouts and records of tests and procedures are to be kept in a secure and safe place throughout the study. Once the study is completed, the records will be kept as required by local regulations, but in no case less than the period defined above.
The Investigator will not relocate or dispose of any study documents before obtaining sponsor's written permission.
Documentation should be kept so as to make its retrieval easy should an audit take place.
All study documentation will be kept locked under the Investigator's responsibility.

14.5 Reports

Study reports include a Final Report that will be issued by the Sponsor. Report format will be designed by the Sponsor.
All study reports will be signed by the Principal Investigators approving its contents, analysis, results and conclusions.
AE related reporting requirements are specified above.

15. Monitoring Plan

15.1 General Considerations

Monitoring functions will be performed in compliance with Good Clinical Practices, EN ISO 14155, and as outlined in 21CRF§812.43(d) and 21CRF§812.46. InMode MD Ltd procedures detail monitoring procedures and monitor responsibilities.
The study will be monitored periodically, per Sponsor discretion and site monitoring plan, for the purposes of: a) verifying compliance to the protocol and applicable regulations, and b) verifying correspondence of CRF data to original entries in source files.

15.2 On-Site Visits

Periodic on-site monitoring visits are intended to assess the Investigator's adherence to the protocol, maintenance of records and reports, and review of source documents for accuracy, completeness, and legibility, and monitoring of Adverse Events.
During periodic visits the monitor is required to:

- Assess the progress of the study towards meeting study objectives.
- Identify any concerns that stem from observations of device performance and/or review of the subject's CRF, study management documents, and informed Consent documents.
- Monitor AE reporting and investigations.

Reports of on-site visits will be submitted by the monitor and will include, as applicable, resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and corrective actions. Visits may be performed using a video conference or phone call and will not be actual physical visits.

15.3 Site Initiation Meeting

A Site Initiation visit will take place prior to initiation of study procedures. All study related documents and procedures will be explained to all staff involved in the study to ensure understanding of the study requirements.

15.4 Adverse Event Reporting and Follow-up

Monitoring of adverse events, their follow up and outcomes will take place at each study visit.

15.5 Site Closure Visit

Upon approval of the Final Report, a Site Closure Visit will be conducted to ensure that all used and unused devices have been returned to the Sponsor, all relevant documentation is filed and archived under the Investigator's responsibility according to regulations.

16. Data analysis.

16.1 Analysis Sets

- Safety Analysis Set
  The safety analysis set will include all subjects using treatment procedures at least a single time.
- Performance Analysis Set
  Performance analysis set will consist of all subjects providing at least one post treatment performance measurement.
- Treatment of Missing Values
  Only observed data will be used; i.e. missing data will not be imputed.

16.2 Statistical Analysis

Means, and standard deviations for each characteristic will be calculated. Paired sample t-test will be computed to assess changes in before treatment and follow-up scores. Statistical significance will be calculated and two-tail significance level of 0.05 will be used. All analyses will be conducted using IBM SPSS 21.0.

17. References

1. Paul M, Blugerman G, Kreindel M, Mulholland RS. Three dimensional radiofrequency tissue tightening: a proposed mechanism and applications for body contouring. Aesth Plast Surg. 2011;35(1):87-95.

2. Mulholland RS. Nonexcisional, minimally invasive rejuvenation of the neck. Clin Plast Surg. 2014;41:11–31.
3. Chia CT, Theodorou SJ, Hoyos AE, Pitman GH. Radiofrequency-assisted liposuction compared with aggressive superficial, subdermal liposuction of the arms: a bilateral quantitative comparison. Plast Reconstr Surg Glob Open. 2015;3(7):e459.
4. Theodorou SJ, Del Vecchio D, Chia CT. Soft tissue contraction in body contouring with radiofrequency-assisted liposuction: a treatment gap solution. Aesth Surg J 2018, Vol 38(S2) S74–S83.
5. Ahn DH, Mulholland RS, Duncan D, et al. Non-excisional face and neck tightening using a novel subdermal radiofrequency thermocoagulative device. J Cosmet Dermatol Sci Appl. 2011;1:8845–8851.
6. Divaris M, Blugerman G, Paul MD. Face expressive lifting (FEL): an original surgical concept combined with bipolar radiofrequency. Eur J Plast Surg. 2013;DOI 10.1007/s00238-013-0908-2.
7. Keramidas E, Rodopoulou S. Radiofrequency-assisted liposuction for neck and lower face adipodermal remodeling and contouring. Plast Reconstr Surg Glob Open. 2016;4(8):e850.
8. Barry E. DiBernardo, MD; Gordon H. Sasaki, MD; Bruce E. Katz, MD; Joseph P. Hunstad, MD, FACS; Christine Petti, MD, FACS; and A. Jay Burns, MD A Multicenter Study for Cellulite Treatment Using a 1440-nm Nd:YAGWavelength Laser with Side-Firing Fiber. Aesthetic Surgery Journal 2016, Vol 36(3) 335–343

18. Investigator Study Acknowledgment

Investigator's Statement:

I have read and understand the foregoing protocol and any corresponding amendments entitled: "*Clinical Evaluation of Safety and Efficacy of The CelluTite Treatment*.", Study No.: DO608110C, and agree to conduct the Study as outlined herein.

Investigator's Name (Please print)	Investigator's Title

Investigator's Signature	Date

Appendix I: Time and Events Schedule

Visit type **Procedure**	**Visit 1*** Screening Baseline Measures & 1st Treatment	**Visit 2** 1 Week Follow-up	**Visit 3** 1 Month Follow-up	**Visit 4** 3 Months Follow-up	**Visit 5** 6 Months Follow-up
Medical History and Demographics	√				
Inclusion/Exclusion Criteria	√				
Informed Consent	√				
Photos	√	√	√	√	√
Optional: QuantifiCare Photos	√				√
Treatment	√				
Investigator Assessments	√	√	√	√	√
AE**Query	√	√	√	√	√
Concomitant Medication	√	√	√	√	√
Study End					√

* Screening and treatment may occur on the same day and up to 3 weeks interval

** AE – Adverse Events