Safety and Efficacy of Trim II for Non-invasive Lipolysis and Circumference Reduction of Abdomen

NCT05398159

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Study Name: Safety and Efficacy of Trim II for Non-invasive Lipolysis and Circumference Reduction of Abdomen.

Protocol No.: DO609924A

Sponsor: InMode Ltd.

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Revision Log:

Revision #	Date	Modification
A	January 2021	First Release
B	June 2022	

1. Protocol Synopsis

Study Title	Safety and Efficacy of Trim II for Non-invasive Lipolysis and Circumference Reduction of Abdomen.
Protocol No	DO609924A
Sponsor	InMode Ltd.
Investigational Product	Trim II hands free device.
Study Design	Prospective, open label clinical study.
Principle Investigator and Study Site	Site 01: Site 02: Site 03: Site 04: Site 05:
Patient Population and Sample Size	At least 70 female and male subjects, from 5 investigational sites, aged 18-70 seeking non-invasive lipolysis and circumference reduction of abdomen will be enrolled.
Study Duration	Eligible subjects will receive 3 bi-weekly treatments (once in 2 weeks) with Trim II hands-free applicator belt according to the study protocol. Trim II hands-free applicator composed of 4 units applied to the abdominal area, using a single-use belt. Each treatment duration will be 45-60 minutes. Study duration for each subject is approximately 6 months (including screening, 3 treatments and 2 follow-up visits at 1 and 3 months post last treatment). Histological samples will be taken from treated area of 8-10 subjects (in total) at baseline and at 3 months follow-up visit. Overall study duration will be approximately 12 months, depending on the subject recruitment rate.

Endpoints	Primary Endpoints: • Efficacy of the Trim II treatment for lipolysis and abdominal circumference reduction. Evaluation of change in abdomen circumference using tape measurements in cm at the 3 months follow-up visit comparing to baseline. Success criteria: Statistically significant reduction in abdominal circumference tape measurements at the 3 months follow-up visit compared to baseline • Safety of the Trim II treatment for lipolysis and abdominal circumference reduction. The occurrence of adverse events will be followed throughout the whole study. Observation, assessment and recording of potential reactions by the investigator. Evaluations will be done immediately after each treatment and at the follow-up visits. The frequency, severity and causality of reactions will be recorded. Secondary Endpoints: • Efficacy of the Trim II treatment for fat and circumference reduction in abdomen, as assessed by two blinded evaluators. Evaluation of photographs at baseline and 3 months follow-up. Success criteria: Correct identification of baseline and 3-month follow-up visit photographs in at least 70% of treated subjects by two blinded evaluators. • Change in abdominal fat thickness measured by ultrasound imaging (USI) at the 3 months follow-up visit comparing to baseline. Success criteria: statistically significant change in fat thickness measurements at the 3 months follow-up visit compared to baseline. • Evaluation of change in histological samples at 3 months follow-up visit comparing to baseline. Success Criteria: Effect on fat tissue while the dermal and epidermal layers are intact with no adverse skin events • Subject's satisfaction with study treatment at 3 months follow-up visit. Subject's satisfaction with the therapy results evaluated through the Subject Satisfaction Questionnaire (5-point scale). • Treatment comfort during the study treatment. Subjects will be asked to rate discomfort using Subject's discomfort (pain) level after each treatment evaluated using the Therapy Comfort Questionnaire
Visits	Each subject will undergo at least 5 study visits including: screening, 3 treatments and 2 follow-up visits. Duration of each treatment visit is approximatly 2 hours. ***Visit 1:*** Screening, baseline and 1st treatment (can occur on th same day)

	- Screening will be performed to determine subject eligibility as well as to collect the required medical information and obtain signed Informed Consent - Baseline abdominal fat thickness measured by ultrasound - Baseline photographs of treatment area - Baseline weight and hight (BMI calculation) - Baseline circumference tape measurement - Baseline caliper measurement - Baseline histologies (8 subjects) - Abdominal 1st treatment will be done using the TRIM II hands-free applicators belt according to IFU - Therapy Comfort Questionnaire * Treatment may occur on the same day of screening or within 3 weeks following screening. **Visits 2-3:** 2nd , 3rd treatments – each 2 weeks following previous visit - Weight and height (BMI calculation) - Circumference tape measurement - Caliper measurement - Abdominal treatment will be done using the TRIM II hands-free applicators belt according to IFU - Therapy Comfort Questionnaire **Visit 4:** Follow-up visit – 1 month following last treatment - Treatment area will be photographed - Weight and hight (BMI calculation) - Circumference tape measurement - Caliper measurement **Visits 5:** Follow-up visit – 3 months following last treatment - Treatment area will be photographed - Weight and hight (BMI calculation) - Circumference tape measurement - Caliper measurement - Abdominal fat thickness measured by ultrasound - Histologies (8 subjects) - Subject's satisfaction After each treatment and at all visits, skin response and adverse events will be recorded.
Main Eligibility Criteria	<u>Inclusion Criteria</u> - Female and male subjects, aged 18-70. - BMI≤ 30. - Subjects seeking non-invasive lipolysis and circumference reduction of abdomen - Female should not be pregnant or lactating and must be either post-menopausal, surgically sterilized, or using a medically acceptable form of birth control at least 3

	months prior to enrolment (i.e., oral contraceptives, contraceptive implant, barrier methods with spermicide or abstinence). - In addition, negative urine pregnancy test as tested before each treatment and at the last visit for women with childbearing potential (e.g. not menopause). - General good health confirmed by medical history and skin examination of the treated area. - The subjects should understand the information provided about the investigative nature of the treatment, possible benefits and side effects, and sign the Informed Consent Form, including permission to use photography. - The subjects should be willing to comply with the study procedure and schedule, including the follow up visits, and will refrain from using any other abdominal treatment methods during the entire study period. <u>Exclusion Criteria</u> - Active electrical implant/device in any region of the body, including pacemaker or internal defibrillator - Permanent implant in the treated area such as metal plates, screws or silicon, metal piercing or other. - Current or history of skin cancer, or current condition of any other type of cancer, or pre-malignant moles. - Severe concurrent conditions, such as cardiac disorders, sensory disturbances, epilepsy, uncontrolled hypertension, and liver or kidney diseases. - History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin. - History of bleeding coagulopathies or use of anticoagulants except for low-dose aspirin. - Patients with history of diseases stimulated by heat, such as recurrent Herpes Simplex in the treatment area, may be treated only following a prophylactic regimen. - Impaired immune system due to immunosuppressive diseases such as AIDS and HIV or use of immunosuppressive medications. - Pregnancy and nursing. - Poorly controlled endocrine disorders, such as Diabetes, or thyroid dysfunction and hormonal virilization. - Isotretinoin (Accutane) within last 6 months. - Any active condition in the treatment area, such as sores, Psoriasis, eczema, and rash, open lacerations, abrasions or lesions, infection in the area to be treated. - Any surgical procedure in the treatment area within the last 12 months or before complete healing. - Having received treatment with light, laser, RF, or other devices in the treated area within 2-3 weeks for non-ablative procedures, and 6-12 weeks for ablative fractional

	laser resurfacing (according to treatment severity) prior to treatment, except special recommendations. - Use of non-steroidal anti-inflammatory drugs (NSAIDS, e.g., ibuprofen-containing agents) one week before and after each treatment session, as per the practitioner's discretion. - As per the investigator's discretion, refrain from treating any condition which might make it unsafe for the patient. - Participated in another investigational drug or device study or have completed the follow-up phase for any previous study less than 30 days prior to the first evaluation in this study.

Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants.

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2. Introduction & Study Rationale

Unwanted excess fat is a common medical and aesthetic concern. Surgical interventions may yield definitive results of fat reduction and body contouring, however invasive modalities require long recovery time and may be associated with significant risks.

A variety of non-invasive body treatments are available for medical aesthetic indications such as circumference reduction and fat lipolysis. These include devices based on optical energy such as lasers and Intense Pulsed Light (IPL), devices based on ultrasound technologies, radiofrequency (RF), Cryolipolysis, suction- massage, or combined technologies.

Non-invasive modification of the adipocyte by the various energies involves one of several mechanisms such as thermal augmentation of normal fat metabolic pathways, thermal destruction, cavitational destruction, or creation of a temporary adipocyte cell membrane pore[1]. As a non-invasive option, these technologies have been developed to reduce cellulite and body circumference with minimal recovery time and risks[2]. Through these mechanisms, the final result is that the sizes of the adipocytes are either temporarily or permanently reduced and/or the number of adipocytes is reduced, which will result in a measurable reduction of fat and circumference of the treated area.

RF technology for fat related indications is vastly used and clinically studied. RF delivers a thermal stimulus to the skin and subcutaneous adipose tissue causing neocollagenesis and thickening of the dermis and enhancement of lipolysis - fat cell metabolism, resulting in reduction of adipose tissue volume and circumferences[3].

[redacted]

3. Definitions, Acronyms and Abbreviations

RF - Radiofrequency

IPL – Intense Pulsed Light

EMS - Electrical Muscle Stimulation

NMES - Neuromuscular Electrical Stimulation

USI – Ultrasound Imaging

AE - Adverse Events

SAEs - Serious Adverse Events

UADEs - Unanticipated Adverse Device Effects

ICF – Informed Consent Form

CRF- Case Report Form

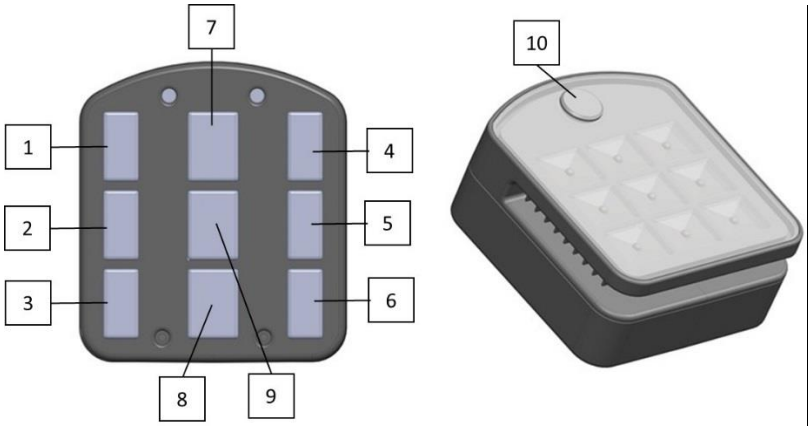
4. Device Description

[redacted]

[redacted]

[redacted]

[redacted]



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Another safety feature is a hand-held switch (Figure 2) that interrupts the treatment process and switches the system to pause state until the operator re-enables it. The patient can use the hand-held switch to pause the treatment if the discomfort becomes excessive.

5. Study Objectives

The Primary Objective of this trial is to evaluate the safety and efficacy of the Trim II treatment for lipolysis and abdominal circumference reduction.

6. Study Endpoints

6.1 Primary Endpoints

- Efficacy of the Trim II treatment for lipolysis and abdominal circumference reduction.
  Evaluation of change in abdomen circumference using tape measurements in cm at the 3 months follow-up visit comparing to baseline.
  Success criteria: Statistically significant reduction in abdominal circumference tape measurements at the 3 months follow-up visit compared to baseline.
  * The primary effectiveness endpoint will be calculated based on those patients whose weight remains stable during the study period. A subject is defined as having maintained her weight during the treatment period if it remained within ±3% (inclusive) of baseline for the respective period.

- Safety of the Trim II treatment for lipolysis and abdominal circumference reduction.
  The occurrence of adverse events will be followed throughout the whole study. Observation, assessment and recording of potential reactions by the investigator.
  Evaluations will be done immediately after each treatment and at the follow-up visits. The frequency, severity and causality of reactions will be recorded.

6.2 Secondary Endpoints

- Efficacy of the Trim II treatment for fat and circumference reduction in abdomen, as assessed by two blinded evaluators. Evaluation of photographs at baseline and 3 months follow-up.
  Success criteria: Correct identification of baseline and 3-month follow-up visit photographs in at least 70% of treated subjects by two blinded evaluators.
- Change in abdominal fat thickness measured by ultrasound imaging (USI) at the 3 months follow-up visit comparing to baseline.
  Success criteria: statistically significant change in fat thickness measurements at the 3 months follow-up visit compared to baseline.
- Evaluation of change in histological samples at 3 months follow-up visit comparing to baseline.
  Success Criteria: Effect on fat tissue with no adverse effect in dermal tissue
- Subject's satisfaction with study treatment at 3 months follow-up visit.
  Subject's satisfaction with the therapy results evaluated through the Subject Satisfaction Questionnaire (5-point scale) as follows: +2 = Very satisfied; +1 = Satisfied; 0 = Indifferent; -1 = Disappointed; -2 = Very disappointed.
- Therapy comfort during the study treatment.
  Subjects will be asked to classify skin reactions (subjective evaluation) and will rate discomfort using visual analog pain scale from 0 (no pain) to 10 (intolerable pain) immediately after each treatment session.

7. Study Population

7.1 General Considerations

The study will recruit at least 70 female and male subjects aged 18-70 of skin seeking non-invasive lipolysis and circumference reduction, in 5 sites.

Treatment area: abdomen

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 Subject Withdrawal and Replacement

Subjects enrolled in the study can discontinue their participation at any time for any reason without prejudice or reduction in the quality of their medical care. The investigators or sponsor can terminate a

subject's participation in this study to protect the subject's health or if the subject fails to follow directions resulting in noncompliance to study procedures. Subjects who withdraw or are terminated from the study may be replaced to ensure that at least 70 subjects have completed the study. Subjects who fail to complete the treatment will be replaced and will not be evaluable.

7.3 Subject Identification

A unique subject identification code will be assigned when an individual subject is qualified for enrolment.

Subject identification details will be coded using subject's initials, site number and subject case number. Subject initials will be composed of the first letter of given name, first letter of middle name and first letter of family name (for example, ADS for Adam Daniel Smith) and a three-digit sequential number. The investigator will complete subject identification on a confidential site log, which will be used for the purposes of traceability.

An example is provided below:

ADS 101

In any case, other identification details (i.e. full names, phone numbers, etc,) will not be filled in any way in the Case Report Files. The identification log will be kept in the study file only.

7.4 Inclusion Criteria

- Female and male subjects, aged 18-70.
- BMI≤ 30.
- Subjects seeking non-invasive lipolysis and circumference reduction of abdomen
- Female should not be pregnant or lactating and must be either post-menopausal, surgically sterilized, or using a medically acceptable form of birth control at least 3 months prior to enrolment (i.e., oral contraceptives, contraceptive implant, barrier methods with spermicide or abstinence).
- In addition, negative urine pregnancy test as tested before each treatment and at the last visit for women with childbearing potential (e.g. not menopause).
- General good health confirmed by medical history and skin examination of the treated area.
- The subjects should understand the information provided about the investigative nature of the treatment, possible benefits and side effects, and sign the Informed Consent Form, including permission to use photography.
- The subjects should be willing to comply with the study procedure and schedule, including the follow up visits, and will refrain from using any other abdominal treatment methods during the entire study period.

7.5 Exclusion criteria

- Active electrical implant/device in any region of the body, including pacemaker or internal defibrillator
- Permanent implant in the treated area such as metal plates, screws or silicon, metal piercing or other.

- Current or history of skin cancer, or current condition of any other type of cancer, or pre-malignant moles.
- Severe concurrent conditions, such as cardiac disorders, sensory disturbances, epilepsy, uncontrolled hypertension, and liver or kidney diseases.
- History of skin disorders, keloids, abnormal wound healing, as well as very dry and fragile skin.
- History of bleeding coagulopathies or use of anticoagulants except for low-dose aspirin.
- Patients with history of diseases stimulated by heat, such as recurrent Herpes Simplex in the treatment area, may be treated only following a prophylactic regimen.
- Impaired immune system due to immunosuppressive diseases such as AIDS and HIV or use of immunosuppressive medications.
- Pregnancy and nursing.
- Poorly controlled endocrine disorders, such as Diabetes, or thyroid dysfunction and hormonal virilization.
- Isotretinoin (Accutane) within last 6 months.
- Any active condition in the treatment area, such as sores, Psoriasis, eczema, and rash, open lacerations, abrasions or lesions, infection in the area to be treated.
- Any surgical procedure in the treatment area within the last 12 months or before complete healing.
- Having received treatment with light, laser, RF, or other devices in the treated area within 2-3 weeks for non-ablative procedures, and 6-12 weeks for ablative fractional laser resurfacing (according to treatment severity) prior to treatment, except special recommendations.
- Use of non-steroidal anti-inflammatory drugs (NSAIDS, e.g., ibuprofen-containing agents) one week before and after each treatment session, as per the practitioner's discretion.
- As per the practitioner's discretion, refrain from treating any condition which might make it unsafe for the patient
- Participated in another investigational drug or device study or have completed the follow-up phase for any previous study less than 30 days prior to the first evaluation in this study.

8. Study Procedures

Each subject will undergo at least 5 study visits including: screening, 3 treatments and 2 follow-up visits. Duration of each treatment visit is approximatly 2 hours.

The Time and Events Schedule is provided in Appendix 1.0.

8.1 Visit 1: Screening, baseline and 1st treatment

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 RF and EMS technologies 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.

The subject will review the informed consent form and the study will be explained to the subject including risks, potential benefits, procedures, visit requirements, and other alternative treatment options. If the subject qualifies and wishes to participate, he/she will complete the ICF with a signature and date. The original will be retained with subject's records and a copy will be provided to the subject. Subjects will then be screened for study eligibility according to inclusion and exclusion criteria.

The following Demographic and Baseline Measurements will be performed:

Screening:

- Demographic data including gender, age, race, skin type (Fitzpatrick scale).
- ICF - Prior to any study procedures, informed consent will be obtained. When the subject fully understands the possible benefits and risks of the study, the subject will be asked to sign and date the informed consent form (ICF). The subject will be given a copy of the signed ICF.
- Subject ID - subjects will be assigned a study subject ID number.
- Medical History - A medical history will be obtained to determine if the subject meets the study criteria, including a list of all prescribed and over the counter medications taken within the previous 6 months will be recorded.
- Pregnancy Screen - Subjects who are capable of becoming pregnant will undergo a urine pregnancy test. This will be repeated prior to all treatments, and at the end of the study (last FU visit, 3-month FU).
- Weight and hight (BMI calculation)
- Pregnancy Urine Test prior to the treatment

Baseline:

- Baseline abdominal fat thickness measured by ultrasound. Appendix 2.0
- Baseline photographs of treatment area - Photography – Baseline photographs will be obtained using a consistent camera and subject placement settings with a digital imaging system. Appendix 3.0
- Baseline circumference tape measurement. Appendix 4.0
- Baseline caliper measurement
- Baseline histologies (8 subjects – at selected sites).

Treatment:
- 1st abdominal treatment will be done using the TRIM II hands-free applicators belt according to IFU
- Subject Comfort Assessment
- * Treatment may occur on the same day of screening or within 3 weeks following screening.
- If the Screening and Treatment procedures are not conducted on the same day, the urine pregnancy test will be repeated on the first treatment day.

<u>Treatment procedure:</u>

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

[redacted]

- [redacted].

After treatment:

- Observation, assessment and recording of adverse events will be conducted.
- Subject will complete Therapy Comfort Questionnaire

8.2 Visits 2-3: 2nd , 3rd treatments , every 2 weeks following previous visit

- Pregnancy Urine Test prior to the treatment
- Weight and hight (BMI calculation)
- Circumference tape measurement
- Caliper measurement
- Abdominal treatment will be done using the TRIM II hands-free applicators belt according to IFU

- Therapy Comfort Questionnaire

8.3 Visit 4: Follow-up visit – 1 month following last treatment

- Treatment area will be photographed
- Weight and hight (BMI calculation)
- Circumference tape measurement
- Caliper measurement

8.4 Visit 5: Follow-up visit – 3 months following last treatment

- Treatment area will be photographed
- Pregnancy Urine Test prior to the treatment
- Weight and hight (BMI calculation)
- Circumference tape measurement
- Caliper measurement
- Abdominal fat thickness measured by ultrasound
- Histologies (8 subjects)
- Subject's satisfaction

After each treatment and at all visits, any adverse events will be recorded.

8.5 Table 1 – Clinical Evaluation Measurements and Tools

Measurement	When to conduct	Method
Height	Baseline, Prior to every treatment and at follow-up's visits	Scale
Weight		Scale
BMI		Calculation
Circumference	Baseline, Prior to every treatment and at follow-up's visits	Tape Measurement (Appendix 4.0)
Caliper	Baseline, Prior to every treatment and at follow-up's visits	Caliper
Photographs	Baseline, and at follow-up's visits	Standardized digital photographs (Appendix 3.0)
Urine pregnancy test	Baseline, Prior to every treatment and at last follow-up visit (3 months)	Urine pregnancy test
Ultrasound imaging	Baseline and last follow-up visit	Abdominal US (Appendix 4.0)
Histology (8 subjects)	Baseline and last follow-up visit	Biopsies taken from treatment areas
Therapy Comfort	After every treatment	Therapy Comfort Questionnaire (Appendix 5)
Immediate response assessment	Immediately after each treatment	Complete in CRF
Subject satisfaction	Last follow-up visit	Subject Satisfaction Questionnaire (Appendix 5)
Safety- AE	During treatment and throughout study.	Examination of skin in the treated area, interview subjects, Adverse Events form, Occurrence and Severity Ratings, as well as relation to treatment, action taken and outcome

9. Adverse Events Reporting

9.1 Definitions

Adverse Event:

An adverse event (AE) is any adverse change in health or side effect that occurs in a study participant during their participation in the study.

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 (Table 2):

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 (Table 3):

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

9.2 Anticipated Adverse Events in this Clinical Evaluation

Possible Trim II adverse effects include but are not limited by:

- Pain

- Excessive redness (erythema)
- Swelling (edema)
- Muscles spasm
- Treatment area infection
- Skin irritation and burns beneath the electrodes have been reported with the use of pain
- Skin burn
- Pigmentation change
- Scar

*Erythema and edema lasting not longer than 24h is typical skin reaction to the treatment.

*Skin irritation and burns beneath the electrodes have been reported with the use of powered muscle stimulators.

9.3 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 above-mentioned risks.

9.4 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

9.5 Investigator Reporting of AEs

The Investigator will report all serious adverse events (SAEs) to InMode Ltd by telephone as soon as becoming aware of them. A written follow-up report will be emailed or faxed to InMode 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 Ltd by telephone within 24 hours. A written follow-up written report will be emailed or faxed to InMode 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 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.

10. Regulatory Aspects

10.1 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, GA 30339, Toll-Free: (888) 636-1062, Phone: (770) 690-9491, Fax: (770) 690-9492 before the start of the study.

10.2 Informed Consent

An Informed Consent that includes all 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 or 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 in accordance with ICH E6R2 guidance. A copy of the IRB approved ICF will also be provided to the subject.

10.3 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. 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.

10.4 Product Supply and Maintenance

The device will be maintained by the Sponsor, as needed. It will be supplied to the participating clinic. The device will be used according to the instructions of the Sponsor and manufacturer, InMode. At the end of

this study, any materials provided specifically for use in this study may be returned to the Sponsor, as described in the Clinical Trial Agreement and study budget.

10.5 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 subject number and study 2-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.

10.6 Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, regulatory authorities, and members of the Research Ethics Committee.

11. Documentation

11.1 Case Report Forms (CRFs)

Paper case report forms will be used in this trial. All protocol-required information collected during the study must be entered in the appropriate field of the case report form (CRF). The investigator, or designated representative, should complete the appropriate CRF fields as soon as possible after information is collected. The information must match the information that exists as source documents in the clinic chart, hospital chart, and/or investigator's files. An explanation should be given for all missing data.

It is the investigator's responsibility to assure the accurate completion, review, and approval of all CRFs and the timely completion and submission of all adverse event forms.

11.2 Maintenance and Retention of Records

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

Printouts provided on thermal paper should be immediately photocopied for long-term storage.

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.

11.3 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.

12. Monitoring Plan

12.1 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 Ltd procedures detail monitoring procedures and monitor responsibilities.

The study will be monitored by the sponsor periodically at the site, per Sponsor discretion.

12.2 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. Some 'visits' may be performed using a video/conference call and will not be actual physical visits.

12.3 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. Suitability of potential study subjects will also be evaluated prior to their inclusion.

12.4 Adverse Event Reporting and Follow-up

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

12.5 Site Closure Visit

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

13. Risk/Benefit Analysis

13.1 Expected Risks:

As indicated in section 9.2 possible Trim II applicator adverse effects include but are not limited by:

- Pain
- Excessive redness (erythema)
- Swelling (edema)
- Muscles spasm
- Treatment area infection
- Skin burn
- Pigmentation change
- Scar

*Erythema and edema lasting not longer than 24h is typical skin reaction to the treatment.

*Skin irritation and burns beneath the electrodes have been reported with the use of powered muscle stimulators.

These risks are minimal when compared to other methods of lipolysis and circumference reduction that are being utilized (such us surgical liposuction).

13.2 Expected Benefits:

The expected benefit of using the Trim II is achieving the desired lipolysis and circumference reduction via a non-invasive technique. As previously indicated, individuals seeking body contouring are currently most likely to do so via liposuction. It is obvious that the low risk profile of the Trim II greatly benefits the individual seeking such treatments as it significantly minimizes the risks associated with the procedure.

13.3 Conclusion:

It can therefore be claimed that the expected benefits associated with the use of the Trim II outweigh its risks.

14. Data analysis

14.1 Analysis Sets

- Safety Analysis Set

The safety analysis set will include all subjects using Embrace 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.

14.2 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.

15. Data Management Plan

Case Report Forms and questionnaires will be retrieved by Monitors after source data verification and resolution of monitoring queries. Documents will be delivered to InMode Ltd onsite data management facility where forms will be logged in, and then data will be entered using a double entry method.

16. References

1. Mulholland RS, Paul MD, Chalfoun C. Noninvasive Body Contouring with Radiofrequency, Ultrasound, Cryolipolysis, and Low-Level Laser Therapy. Clin Plastic Surg 2011 38: 503–520.
2. 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.
3. Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. Lasers Med Sci 2014 29:1627–1631.
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6. Alon G, Frederickson R, Gallager L, Rehwoldt CT, Guillen M, Putnam Pement ML, et al. Electrical stimulation of the abdominals: the effects of three versus five weekly treatments. J Clin Electrophysiol 1992;4:511
7. Alon G, Taylor DJ. Electrically elicited minimal visible titanic contraction and its effect on abdominal muscles strength and endurance. Eur J Phys Med Rehab 1997;7:2-6

17. Investigator Study Acknowledgment

Investigator's Statement:

I have read and understand the foregoing protocol and any corresponding amendments entitled: "Safety and Efficacy of Trim II for Non-invasive Lipolysis and Circumference Reduction of Abdomen", Study No.: DO609924A and agree to conduct the Study as outlined herein.

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

Appendix 1.0: Time and Events Schedule

Visit type **Procedure**	**Visit 1*** Screening Baseline Measures	**Visit 2** **Tx1 (same day or within 21 days after screening)**	**Visit 3** **Tx2 (14 days after Tx1 +/- 2 days)**	**Visit 4** **Tx3 (14 days after Tx2 +/- 2 days)**	**Visit 5** 1 Month Follow-up **(30 days after Tx3 +/- 7 days)**	**Visit 6** 3 Month Follow-up **(90 days after Tx3 +/- 10 days)**
Medical History and Demographics	√					
Physical Exam	√					
Skin type	√					
Pregnancy Screening	√	√	√	√		√
Inclusion/Exclusion Criteria	√					
Informed Consent	√					
Photos	√				√	√
BMI/Height/Weight	√		√	√	√	√
Circumference	√		√	√	√	√
Caliper	√		√	√	√	√
Ultrasound	√					√
Histology-8 subjects (At selected sites)	√					√
Treatment		√	√	√		
Subject's Comfort		√	√	√		
Subject's Satisfaction						√
Skin response and AE		√	√	√	√	√
Concomitant Medication	√	√	√	√	√	√
Study End						√

* Screening and 1st treatment may occur on the same day and up to 3 weeks interval

Appendix 2.0. Measuring Fat Thickness at the Treated Area using Ultrasound Imaging (USI) Device

- At screening visit, the therapist will mark the rectangle of the treatment area according to the applicators setting with white pencil.
- Two US measurement points will be selected and images will be captured (according to the applicators positioning)
- A transparency will be created at baseline for each patient, with treated area, identification marks (umbilicus, spots/moles) and the measurements points marked, to ensure USI of the same point at baseline and FU visit.
- US probe should be applied to measure abdominal subcutaneous fat in the area of the two measurement points (identified according to the transparency).
- Each measurement of fat later thickness should be repeated 2 times and an average value will be recorded.

Appendix 3.0: Photography

At each of the specified time points; photographs of the treated areas should be taken by investigator or their designee.

- Photographs should be taken in a private room or area of the clinic under controlled conditions, including the distance from the camera to the subject, height of the camera, background, camera positioning, subject's positioning and lighting in order to achieve high-quality before & after sets.
- Consistent lighting- Lighting should be preferably projected from about 45º angle in order to emphasize the treatment area appearance.
- For consistency purposes, the same person should ideally take all study photographs.
- The digital files should follow a consistent standard naming scheme containing subject initials and study ID #, visit or visit date.

Specific photography details:

Area: Abdomen:

Five photographs should be taken at each specified time point

- Front
- 45º from the right side
- 90º from the right side
- 45º from the left side
- 90º from the left side

The subject's arms should remain out of the way; it is best to either cross them over each other in front of the chest or hold them up at a 90° angle to the body, ensuring that they do not rest on the chest or touch the body and that they do not cast a shadow in the photograph.

Appendix 4.0: Circumference Measurements

The following steps are necessary to achieve consistent measurements:

- The measurement tape should be parallel to the floor during the measurement
- Prior to circumference measurement, mark the area to be treated in order to perform the measurements within the defined area for treatment. The area to be measured must be at height that includes the area to be treated.
- Baseline measurement should be taken at the level of the widest part of area (most protruding convexity) – horizontal midline. This height level should be recorded for follow up assessments. Two additional measurements will be taken at 2 inches/5cm above this baseline and 2 inches/5 cm below it.
- The consecutive measurements should be performed at the same height recorded at enrollment. In order to assure that measuring tape is parallel to the floor, several reference points should be marked around the treatment area and the measuring tape should be placed such that it is aligned with them.
- The tape should be placed under the reference points in order to maintain repetitive height of the measurement
- The measurement device should be placed at a constant tension to achieve an exact measurement of the circumference
- The same trained evaluator will preferably perform the circumference measurement to avoid bias in results. In case that evaluator is not available, another trained person will perform the procedure.

The circumference measurement:

- Position the subject next to a fixed height measuring device. Such a device could be a wooden/metal measurement stick, fixed perpendicular to the floor.
- Alternatively, a medical height measuring device will be employed.
- The height reference line should be at the widest part of the marked treatment area (horizontal mid-line).
- This height should be kept as the reference in the follow up throughout all measurements of the same treatment area.
- In order to ensure a reproducible posture, position the subject as close as possible to the measurement stick.
- Arms will be crossed over the chest with hands placed in the opposite axillae. The head will be held up with eyes level and looking straight ahead.

- Have the subject rotate slowly to produce the height reference line. This line should be marked on the skin as the subject rotates. Make sure that the height reference points cover the entire length of the circumference, at front, back and two sides.
- In the subject file, record the height of the horizontal mid-line of the treatment area (the distance from the floor). This will enable the operator to re-measure the subject at the same height in the follow up visits for the evaluation of the change in the circumference.
- Place the measurement tape at the widest part of the marked area. The measurement tape should be placed below the reference line.
- Record the measured circumference in the subject file
- Measure circumference at 2 inches/5 cm above the horizontal midsection of the marked treatment area
- Measure circumference at 2 inches/5 cm below the horizontal midsection of the marked treatment area.

Appendix 5.0: Scales

Subject Satisfaction Questionnaire

Satisfaction Rate	Score
Very Satisfied	+2
Satisfied	+1
Indifferent	0
Disappointed	-1
Very Disappointed	-2

Subject Therapy Comfort Questionnaire

Comfort Rate	Score
Very Comfortable	+2
Comfortable	+1
Indifferent	0
Uncomfortable	-1
Pain	-2

Appendix 6.0: Calliper measurements

- Take two measurements next to the belly button from both sides. If measurements are not the same, record the average
- Pull out the fold of skin with the underlying layer of fat
- Place the jaws of the caliper on the pulled skinfold
- Release the trigger of the caliper so the entire force of the jaws is on the skinfold
- Keep holding firmly the fold of skin with the fingers so that the caliper is measuring just the thickness of the fold of skin
- When the caliper is placed on the skinfold it may move a little and slow down after a few seconds, then the measurement should be taken.
- Note the reading on the scale before releasing any pressure off the calipers.
- Maintain consistency with regards to type of caliper used, landmark site measured