# CBL-514

**Protocol Number: CBL-0201EFP**

# A Phase 2a, Open Label Study to Evaluate the Safety, Tolerability, and Efficacy of CBL-514 Injection for the Treatment of Edematous Fibrosclerotic Panniculopathy (EFP) cellulite

**Authors:** [redacted]

**Development Phase:** Phase 2

**Document Version:** Protocol Version 5.0 Dated 15 Nov 2023

Version History

| Protocol/Amendment Number | Date | Details of Amendment |
|---|---|---|
| Version 1.0 | 21 Jun 2022 | Initial |
| Version 1.1 | 17 Aug 2022 | - Revise and add withdrawal criteria<br>- Indicate the preferable area to treat the EFP and revise injection markup procedure<br>- Add reference images |
| Version 1.2 | 13 Oct 2022 | - Revise the visit window at Stage 1<br>- Revise efficacy objective and endpoint |
| Version 2.0 | 24 Mar 2023 | - Revise the dosage level and injection number in Stage 2<br>- To add subject stopping criteria<br>- To add the detail of contraceptive to the synoposis |
| Version 3.0 | 24 May 2023 | - Revise the Endpoints<br>- To add wording to specify the necessity of the treatment at Visit 3<br>- To revise the definition of Per-Protocol population |
| Version 4.0 | 18 Aug 2023 | - Revise the Endpoints<br>- Correct method of the hCG test at treatment and follow up visits |
| Version 5.0 | 15 Nov 2023 | - Revise the Endpoints |

# PROTOCOL AUTHORIZATION

Title: A Phase 2a, Open Label Study to Evaluate the Safety, Tolerability, and Efficacy of CBL-514 Injection for the Treatment of Edematous Fibrosclerotic Panniculopathy (EFP) cellulite.

As Caliway Biopharmaceuticals Co., Ltd. ('Sponsor') representative, I confirm that the study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product (IP), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP).

[redacted]

Signature

2023.11.15

Date

Yu-Fang Ling / Chief Executive Officer

Print Name / Title

# INVESTIGATOR'S AGREEMENT

**Title:** A Phase 2a, Open Label Study to Evaluate the Safety, Tolerability, and Efficacy of CBL-514 Injection for the Treatment of Edematous Fibrosclerotic Panniculopathy (EFP) cellulite.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s) (IB), electronic Case Report Forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Regulatory Board (IRB). No changes will be made to the study protocol without the prior written approval of the Sponsor and the Ethics Committee, except where necessary to avert an immediate hazard to the participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles of the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and applicable local regulatory requirements. The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice (GCP) ICH E6 (R2).

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

_____

Investigational Site

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

# 2. SYNOPSIS

**Name of Sponsor/Company:**
Caliway Biopharmaceuticals Co., Ltd.

**Name of Investigational Product:**
CBL-514

**Name of Active Ingredient:**
[redacted]

**Protocol Number:**
CBL-0201EFP

**Title of Study:**
A Phase 2a, Open Label Study to Evaluate the Safety, Tolerability, and Efficacy of CBL-514 Injection for the Treatment of Edematous Fibrosclerotic Panniculopathy (EFP) cellulite

| **Studied Period (Years):** | **Phase of Development:** |
|---|---|
| Estimated date first participant enrolled: Q1 2023<br>Estimated date last participant completed: Q3 2023 | 2a |

**Objectives:**

**Efficacy Objectives:**

Stage 1:

Primary efficacy:

- To evaluate the improvement of edematous fibrosclerotic panniculopathy (EFP) measured by cellulite severity scale from baseline following administration of 1 course of CBL-514.

Stage 2:

Primary efficacy:

- To evaluate the improvement of EFP measured by cellulite severity scale from baseline following of at least 1 course administration of CBL-514.

Secondary efficacy:

- To evaluate the response rate of EFP improvement by Global Aesthetic Improvement Scale (GAIS) reported by the clinician and participant, respectively, following the administration of at least 1 course of CBL-514.

**Safety and Tolerability Objectives:**

Stage 1:

- To evaluate safety and tolerability following administration of 1 course of CBL-514.

Stage 2:

- To evaluate safety and tolerability following administration of at least 1 course of CBL-514.

**Endpoints:**

**Efficacy Endpoints:**

Stage 1:

Primary efficacy:

- Change in total scores from baseline according to the modified Hexsel cellulite severity scale (CSS) at V4 and V5.

Secondary efficacy:

- Percentage of participants' thighs that achieve at least 1-level severity improvement determined by the total scores of modified Hexsel CSS at V4 and V5 compared to baseline.

Stage 2:

Primary efficacy:

- Change in total scores according to the modified Hexsel CSS at V4.

Secondary efficacy:

- Percentage of participants' thighs with at least 1-level severity improvement determined by the total scores of modified Hexsel CSS at V4 and V5 compared to baseline.
- Change in total scores according to the modified Hexsel CSS at V5.
- Percentage of participants' thighs with achieve at least 2-score improvement in modified Hexsel CSS at V4 and V5.
- Percentage of participants with improvement in GAIS assessed by the clinician and participant, respectively.

**Safety and Tolerability Endpoints:** Stage 1 and Stage 2:

- Safety and tolerability endpoints will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Assessments will be inclusive of:
  - adverse events and treatment-emergent adverse events,
  - adverse events and treatment-emergent adverse events at the injection site(s),
  - adverse events and treatment-emergent adverse events related to the investigational product (IP),
  - adverse events of special interest,
  - clinically significant laboratory findings including hematology, biochemistry, coagulation, and urinalysis tests,
  - clinically significant abnormalities in physical examination, 12-lead electrocardiogram parameters and vital signs, and
  - use of concomitant medications to treat treatment-emergent adverse events (TEAEs).

**Methodology:**

**Study Design**

This is a 2-stage adaptive design, Phase 2a study to evaluate the safety, tolerability, and efficacy of CBL-514 injection for the treatment of EFP; cellulite. CBL-514 will be injected on the posterolateral thigh, preferably on the lateral side, to treat the EFP (See Section 20.1 Appendix 1). This Phase 2a study has an integrated design consisting of a single ascending dose (SAD) part in Stage 1 followed by a single-arm design in Stage 2. Participants that enroll in Stage 1 of the study will not be eligible to take part in Stage 2 of the study.

A total of up to 32 participants (n = 12 in Stage 1; n = 20 in Stage 2) with moderate or severe EFP will be enrolled. Cellulite improvement will be evaluated by the Investigator (or designee) by using a modified Hexsel CSS (Hexsel and Dal'Forno 2009). The GAIS assessment will be reported by the clinician and participant, respectively, to evaluate the respond rate of cellulite improvement.

Hexsel CSS is composed of 5 key morphological aspects which includes (A) the number of depressions, (B) depth of depressions, (C) clinical appearance of evident raised lesions, (D) the presence of flaccidity, and (E) the classification scale originally described by Nürnberger and Müller (Nurnberg and Muller 1978). The severity of cellulite in this study will be assessed using a modified Hexsel CSS. This modified Hexsel CSS is based on the following descriptors:

[redacted]

The severity level of cellulite will be scored as mild, moderate, or severe which will be determined by the total scores obtained from items A to C as illustrated in Synopsis Table 1.

**Synopsis Table 1: Scoring System of Cellulite Severity**

| Cellulite Severity Total Score | Cellulite Severity Level |
|---|---|
| 0 | None |
| 1 to 3 | Mild |
| 4 to 6 | Moderate |
| 7 to 9 | Severe |

The GAIS is a 5-point scale rating aesthetic improvement in appearance, compared with pretreatment, as judged by the clinician and participant, respectively. The rating categories are 'worse', 'no change', 'improved', 'much improved', and 'very much improved'.

**Stage 1 (single dose escalation, open label)**

The Stage 1 will include a total of 12 participants enrolled in 3 sequential escalating CBL-514 dose groups: 1.0 mg/cm$^2$, 1.5 mg/cm$^2$, and 2.0 mg/cm$^2$. The groups will be open label and each group will enroll 4 participants.

Eligible participants will be sequentially assigned to receive 1 course of allocated CBL-514 dose administered by subcutaneous injection on both sides of the posterolateral thighs on Day 1. When the IP is administered, the number of injections per posterolateral side of the thigh does not need to be distributed equally. The dosing scheme is presented in Synopsis Table 2.

**Synopsis Table 2: Dosing Scheme – Stage 1 (note: the concentration of CBL-514 is [redacted])**

| Group | Dose Level (mg/cm$^2$) | Injection Volume per 1 cm$^2$ Grid | Administration for 1 course | | |
|---|---|---|---|---|---|
| | | | Total No. of Injections | Total Injection Volume (mL) | CBL-514 (mg) |
| 1 | 1.0 | 0.2 mL | 40 | 8 | [redacted] |
| 2 | 1.5 | 0.3 mL | 40 | 12 | [redacted] |
| 3 | 2.0 | 0.4 mL | 40 | 16 | [redacted] |

[redacted] The interval between each injection spots must be at least 1 cm. A detailed description for how the treatment area is to be demarcated will be provided in the IP administration manual.

Prior to administration of the IP, cold compress will be applied to the treatment area. The usage of topical anesthetic cream (5% to 10% lidocaine) prior to administration of the IP will be evaluated before dose escalation to Group 2 and/or Group 3, and will depend on the participant's tolerance to injection site pain during IP administration. The same procedure prior to the IP administration will be adopted in each group, respectively. After the administration, participants will remain in the research unit for observation and until all planned assessments for the visit are completed. Prior to the discharge after treatment, interventional or prophylactic medications (such as analgesics for injection site pain) may be provided to participants at the discretion of the Investigator. Participants will visit

the site at Week 1/Visit 3, Week 2/Visit 4, and Week 4/Visit 5 post dose for safety and efficacy follow-up assessments.

An early termination (ET) visit will be planned if a participant who has received treatment withdraws from the study early. The ET visit will follow the procedures of Stage 1 Week 1/Visit 3.

To accompany follow-up assessments, a participant diary will be provided to each participant to record any injection site reactions/changes to the injection site/s or any discomforts post Day 1 (post IP administration) until Visit 5 (EOS). Participants will be instructed to bring the participant diary with them for the designated visits to the clinic.

During Stage 1 of the study, the safety review meeting will be held after 4 participants in a dose group complete the Week 1 visit. The Safety Review Committee (SRC) will review all reported adverse events (AEs), adverse events of special interest (AESIs), and the results of safety assessments of all participants from each dose group. Based upon review of available safety and tolerability data from each preceding dose group, the SRC will make a decision on proceeding to the next dose group.

The safety and tolerability data from Stage 1 will be reviewed by the SRC before commencement of Stage 2. The SRC will decide a recommended dose for Stage 2 of the study. The protocol including the final decision of the Stage 2 dose will be submitted to the Institutional Review Board (IRB) for review and approval before proceeding to Stage 2 of the study.

**Stage 2 (up to 2 courses, single arm study)**

Stage 2 of the study will be initiated after IRB review of the protocol which includes the confirmed Stage 2 dose. Stage 2 will be conducted as a single arm study with one selected CBL-514 dose. The unit dose of CBL-514 used in the Stage 2 will be no higher than the highest safe unit dose from Stage 1.

In Stage 2 of the study, up to 20 participants will be enrolled. Participants that enroll in Stage 1 of the study will not be eligible to take part in Stage 2 of the study. Each participant will receive up to 2 courses of CBL-514 administered by subcutaneous injection on both posterolateral thighs. The IP will be administered on Visit 2 (Day 1) and then at Visit 3 (Visit 2 + 4 weeks [± 7 days]) following the first dose.

The area which is to be treated will be assessed at Screening by the Investigator (or designee). This will include an evaluation of the enrollment criteria for the cellulite severity score and the overall area (coverage) of cellulite. Based on this assessment, the Investigator will make a determination with regards to the injection number for the participant. [redacted] A detailed description for how the treatment area is to be demarcated will be provided in the IP administration manual.

Prior to administering the second treatment with CBL-514 at Visit 3 the Investigator (or designee) will evaluate the severity of EFP assessed by the modified Hexsel CSS items (A), (B), and (C). If the cellulite severity level at the original treatment site of both thighs are assessed as either Mild or None according to the modified Hexsel CSS assessment, the second treatment of CBL-514 will not be administered at Visit 3. Instead these participants will proceed to the follow-up assessments in accordance with Visit 4 procedures and for these participants the second follow-up will be performed at Visit 5, scheduled for 12 weeks (± 7 days) post Day 1 in accordance with Visit 5 procedures. On the other hand, if only one thigh is assessed as either Mild or None according to the modified Hexsel CSS assessment, the second treatment of CBL-514 can still be administrated to the other thigh and the injection number should between 20 to 80.

If the participants complete 2 treatment visits, the first follow-up Visit 4 will be performed 4 weeks (± 7 days) post Visit 3 and the second follow-up Visit 5 will be performed 12 weeks (± 7 days) post Visit 3.

An ET visit will be planned for any participant who has received treatment and withdraws from the study early. The ET visit will follow the procedures of Visit 4.

All study assessments for all visits and follow-up will be conducted as per the Schedule of Assessments.

To accompany follow-up assessments, a participant diary will be provided to each participant to record any injection site reactions/changes to the injection site/s or any discomforts post Day 1 (post IP administration) until Visit 5 (EOS) or when all injection site reactions have resolved or stabilized. Participants will be instructed to bring the participant diary with them for the designated visits to the clinic.

At least 40 injections and up to 160 injections in total will be administered to both posterolateral thighs per treatment. When the IP is administered, the number of injections per posterolateral side of the thigh does not need to be distributed equally. The dosing scheme is presented in Synopsis Table 3.

**Synopsis Table 3: Dosing Scheme – Stage 2**

| Group | Dose Level (mg /cm$^2$) | Injection Volume per 1 cm$^2$ Grid | Administration per Treatment (minimum / maximum) | | |
|---|---|---|---|---|---|
| | | | Total No. of Injections | Total Injection Volume (mL) | CBL-514 (mg) |
| 1 | 2.0 | 0.4 mL | 40 / 160 | 16 / 64 | [redacted] |

Prior to administration of the IP, cold compress will be applied to the treatment area. The usage of topical anesthetic cream (5% to 10% lidocaine) prior to administration of the IP will be evaluated before a participant receives the second treatment, and will depend on the participant's tolerance to injection site pain during the first treatment. Participants will remain in the research unit for observation after the administration of the IP, and until all planned assessments for the visits are completed. Prior to the discharge after treatment, interventional or prophylactic medications (such as analgesics for injection site pain) may be provided to participants at the discretion of the Investigator.

During Stage 2 of the study, if a participant experiences an AESI following the first administration of the IP, the Investigator (or designee) will report the event to Sponsor and Medical Monitor (MM) within 24 hours upon the event being noticed by the Investigator or designee. The SRC will review the safety data of the participant and decide whether the participant experiencing the AESI should proceed with the second course of CBL-514 in Stage 2.

**Adverse Events of Special Interest**

An AESI is any of the following IP-related events.

1. Skin or fat atrophy that extends > 2 cm from an injection point.
2. Severe injection site pain lasting more than 72 hours.
3. Severe injection site bruising.
4. Any skin hyper or hypopigmentation at the target area and/or the surrounding skin lasting for > 4 weeks.
5. Any skin ulceration at the target area and/or the surrounding skin.
6. Any urticaria at the target area and/or the surrounding skin requiring oral treatment, lasting for > 72 hours.
7. Telangiectasia at the target area and/or the surrounding skin lasting for > 7 days.
8. Local numbness and/or paresthesia lasting for > 7 days.

**Stopping Criteria for Overall Study**

Administration of IP may be paused, and all participants will not receive further treatments, until a consultation has taken place between the Investigator, the MM, and the Sponsor representative under the following circumstances:

1. Any participant experiences an adverse event as Grade 3 or higher grade (as defined in the NCI-CTCAE version 5.0) for a cardiovascular, renal, or hepatic event considered to be at least possibly related to IP;
2. Except for cardiovascular, renal, or hepatic events specified in Criterion #1, any participant experiences a Grade 4 or higher clinical or laboratory abnormality (as defined in the NCI-CTCAE version 5.0) considered to be at least possibly related to IP;
3. Any participant experiences a serious adverse event (SAE) that is considered to be at least possibly related to IP;
4. An AE or group of AEs that singularly or in aggregate suggests to the Investigator or Sponsor that the IP is poorly tolerated and further treatment per protocol (PP) may not be safe.

If any one participant meets the stopping criteria for overall study, the study will be suspended from continuing treatment visits for all participants. Participants should remain in the study and be followed until the AE resolves or stabilizes.

If any of these criteria occur, the SRC consisting of the Sponsor representative, the Investigator, and the MM will meet as soon as possible to evaluate the event and decide whether treatment can continue for the rest of the participants.

**Stopping Criteria for Participant**

If a participant experiences any of following circumstances, the participant should not receive additional IP administration. If any of these criteria occur, the event will be reported to the Sponsor and MM within 24 hours upon noticed by the PI or delegates.

1. A Grade 2 or higher grade adverse event (as defined in the NCI-CTCAE version 5.0) for bone marrow or cardiovascular event
2. Except for bone marrow and cardiovascular event specified in Criterion #1 and expected injection site reactions (refer to Investigator Brochure), a Grade 3 or higher grade adverse event (as defined in the NCI-CTCAE version 5.0).

**Withdrawal Criteria**

A participant must be removed from the study at any time, if any of the following criteria are met:

- Participant withdraws consent.
- Participant has body weight change $\geq$ 3kg compared to Day 1 body weight during the whole study period.
- Participant has body weight change $\geq$ 3kg during the follow-up period compared to the body weight from the last treatment visit.
- Any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the participant continuing on the study.

**Number of Participants (Planned):**

A total of 32 participants are planned to be enrolled for the 2-stage study.

Up to 12 participants will be enrolled in 3 sequential dose groups in Stage 1 of the study.

Up to 20 participants will be enrolled in a single dose group in Stage 2 of the study.

The sample size is not based on formal hypothesis testing but is consistent with currently accepted standards for exploratory investigation design.

**Main Criteria for Inclusion:**

To be eligible to enter the study, participants must meet all of the following inclusion criteria:

1. Female aged 18 years to 64 years old (at Screening), inclusive.
2. Have a BMI > 18.5 and < 35 kg/m$^2$ and body weight ≥ 50 kg at Screening and Day 1.
3. The participant has both sides of posterolateral thighs assessed according to the modified Hexsel CSS (A) number of evident depressions, (B) depression depth scale, and (C) morphological appearance of skin surface alterations. On assessment by the modified Hexsel CSS, the participant scores at least 4 and no greater than 8 at Screening and Day 1. The total score must contain:
   a. Hexsel CSS item (A) 'number of evident depressions' score of ≥ 1
   b. Hexsel CSS item (B) 'depth of depressions' score of ≥ 1
4. Participant has a stable lifestyle (e.g., exercise, eating patterns, and smoking habit) per participant report for at least 3 months before Screening and during the study.
5. Voluntarily signs the informed consent form and, in the opinion of the Investigator or delegate, is physically and mentally capable of participating in the study, and willing to adhere to study procedures.

**Main Criteria for Exclusion:**

A participant who meets any of the following exclusion criteria must be excluded from the study:

1. Female participant of childbearing potential who is not willing to commit to an acceptable contraceptive regimen with her partner from the time of Screening and throughout study participation until 90 days after the last IP dose, or who is currently pregnant or lactating. The acceptable contraception are listed as follow.
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation[1]: oral, injectable, implantable
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - sexual abstinence
   - condom used by male partner during sexual intercourse

   Complete details are provided in Section 20.3 Appendix 3.

Note: females who are not of childbearing potential are not required to use contraception. Females not of childbearing potential are defined as those who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are postmenopausal (defined as aged at least 50 years old with ≥ 12 months of amenorrhea and a follicle-stimulating hormone [FSH] > 30 IU/L at Screening).

2. Participant diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation within 14 days prior to the IP administration.
3. Participant has hemoglobin A1c (HbA1c) ≥ 9%, delayed wound healing, or any diabetic risks which, in the opinion of the Investigator (or designee) is inappropriate to participate in the study.
4. Participant has a clinically significant cardiovascular disease and abnormal findings in electrocardiogram (ECG) at Investigator's (or designee's) discretion.
5. Participant with active or prior history of malignancies within 5 years before Screening or being assessed for a possible malignancy. Except adequately treated basal cell carcinoma of the skin and in situ squamous cell carcinoma of the skin would be eligible as per Investigator's (or designee's) discretion.
6. Participant with a history of human immunodeficiency virus (HIV)-1 infection, or participants with active HIV infection at Screening with a positive HIV antigen/antibody (Ag/Ab) combination test.
7. Participant with a history of trypanophobia, the extreme fear of medical procedures involving injections or needles, or who experience vasovagal syncope and pass out at the sight of blood or a needle.
8. Participant with any hepatic medical condition that, in the opinion of the Investigator (or designee), would interfere with assessment of safety or efficacy or compromise the participant's ability to undergo study procedures or provide informed consent.
9. Participant who has a recent history of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication within 6 months prior to Screening.
10. Participant has abnormal skin or local skin conditions at the treatment area, which in the opinion of the Investigator (or designee), is inappropriate to participate in the study. This includes but is not limited to any of the following:
    a. skin manifestations of a systemic disease
    b. any abnormality of the skin or soft tissues on the anticipated treatment area
    c. skin laxity on treatment area when the participant is in the standing position
    d. sensory loss or dysesthesia in the area to be treated
    e. evidence of any cause of enlargement in the area to be treated other than localized subcutaneous fat
    f. tattoos on the area to be treated
    g. participant with a propensity for keloid or hypertrophic scarring.
11. Participant who has had the following surgical or aesthetic procedures:

a. liposuction, cryolipolysis, ultrasonic lipolysis, low level laser therapy (LLLT), or lipolysis injection to the region to be treated before Screening
b. medical device, injection (including but not limited to collagenase clostridium histolyticum injections and collagen stimulating injections), over-the-counter (OTC) cosmetic cream, or cosmetic program to prevent or mitigate EFP to the region to be treated within 12 months before Screening and throughout study participation
c. massage to the region to be treated within 2 weeks before Screening and throughout study participation.

12. Participant is undergoing chronic steroid or immunosuppressive therapy, except for asthma inhaler or topical steroids for skin conditions if the medications are not used on the treatment area.
13. Participating is requiring continual use of the following therapeutic agents during the study: terfenadine, buspirone, fexofenadine, any medication that is known to strongly inhibit or induce CYP enzymes, sensitive CYP substrates or drugs with narrow therapeutic index, which in the opinion of the Investigator (or designee), may affect the evaluation of the investigational product or place the participant at undue risk.

    If a participant needs to use the above-mentioned therapeutic agents during the study for any reason, these therapeutic agents should not be used at least for 2 days before dosing and until 1 day after dosing.
14. Participant receives nonsteroidal anti-inflammatory drug (NSAID) including aspirin within 14 days prior to the IP administration.
15. Participant is unable to receive topical anesthesia (e.g., history of hypersensitivity to lidocaine).
16. Participant with known allergies or sensitivities to the IP or its components.
17. Participant with liver cirrhosis or with inadequate liver function at Screening defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKP), total bilirubin (TBIL), or gamma-glutamyl transferase (GGT) > 3.0 × upper limit of normal (ULN).
18. Participant with any renal impairment, defined as abnormal serum creatinine, and urea > 1.5 × ULN or estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 $m^2$. Participants who are currently on dialysis should be excluded.

    Participants with an eGFR ≥ 60 and < 90 mL/min/1.73 $m^2$ at Screening should be evaluated by the Investigator to exclude pre-existing renal disease or associated dysfunction. If mild decrease in eGFR is assessed by the Investigator as not clinically significant or not related to dysfunction, the participants may be eligible upon the Investigator's assessment.
19. Use of other investigational product or device within 4 weeks prior to Screening.

**Investigational Product, Dosage, and Mode of Administration:**

The IP, CBL-514 is manufactured for subcutaneous injection, presented at a concentration of [redacted] at a total volume of 20 mL per vial. The active ingredients per each mL of solution constitute [redacted] curcumin and [redacted] *trans*-resveratrol.

**Reference Therapy, Dosage, and Mode of Administration:**

There is no reference therapy for this study.

**Duration of Treatment:**

The Screening period is 28 days (Day -28 to Day -1) for both stages of the study.

**Stage 1:**

Each participant will participate in Stage 1 of the study for approximately 5 weeks, including Screening visit, baseline visit on Day 1, and 3 follow-up visits at Week 1, Week 2, and Week 4, respectively.

**Stage 2:**

Each participant will participate in Stage 2 of the study for approximately 20 weeks.

The study periods are set out as follows: Screening (Visit 1), admission/first treatment visit on Day 1 (Visit 2), second treatment visit (Visit 3), and 2 follow-up visits (Visit 4 and Visit 5).

Duration of study participation is defined as the period between the day the participant provides written consent and until all study required examinations have been completed.

**Statistical Methods:**

Complete details of the statistical analyses and methods, including data conventions, will be provided in the statistical analysis plan (SAP). The SAP will be finalized before the database is locked.

Descriptive statistics will be used to summarize the safety and efficacy data. Dose comparisons will be exploratory in nature.

No adjustments will be made for missing or incomplete data, except for missing efficacy data. Missing efficacy data will be imputed using multiple imputation process (MI SAS procedure) with missing at random (MAR) pattern.

The baseline value is defined as the last available result collected/derived prior to the first investigational drug administration. The change from baseline value is defined as the difference between the result at the post-baseline time point and the baseline value.

Descriptive statistics will consist of the number of observations (n), mean, standard deviation (SD), minimum, median, and maximum for continuous data. Where applicable, 95% confidence intervals (CIs) for the mean may be presented.

Categorical data will be summarized using counts and percentages. Unless specially stated otherwise, the denominator of all percentage calculations will be the number of participants in the treatment group for the specific analysis set.

All collected and derived data will be listed.

**Analysis Populations**

**Safety Population**

All participants who receive any amount of study treatment will be included in the Safety Population. The Safety Population will be used for summaries and listings of safety and tolerability.

**Intent-To-Treat Population**

The Intent-to-treat (ITT) Population will include all enrolled participants who received at least 1 course of treatment with the IP and contributed at least 1 post-dose primary efficacy evaluation. The ITT Population will be used for efficacy assessment.

**Per-Protocol Population**

The Per-protocol (PP) Population is a subset of the ITT Population. Participants without any efficacy-related major protocol violations, who completed the required dosing schedules of the IP and planned follow-up visits after treatment (and completed those visits within the designated visit window), and who had stable body weight during the study (defined as body weight change < 3 kg compared to

baseline) will be included in the PP Population. The PP Population will be used to repeat efficacy analysis, as relevant.

**Safety Assessment**

All safety assessments, including AEs, laboratory evaluations, vital signs, ECGs, physical examination, injection site reactions, and other safety assessments, will be analyzed using the Safety Population.

- AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the start of the study. A by-participant AE data listing, including verbatim term, preferred term (PT), system organ class (SOC), treatment, severity, and relationship to IP, will be provided. The number of participants experiencing TEAEs and number of individual TEAEs will be summarized among treatment groups (or sequences), by SOC and PT. TEAEs will also be summarized among treatment groups (or sequences), by severity and by relationship to IP.
- Clinical laboratory tests and vital signs of observed values and changes from baseline will be summarized using descriptive statistics. Physical examination findings, injection site assessments, and ECGs will also be summarized descriptively.

**Efficacy Assessment**

**Modified Hexsel Cellulite Severity Scale**

For the primary endpoint, the total scores in the modified Hexsel CSS (A) number of evident depressions,
(B) depression depth scale, and (C) morphological appearance of skin surface alterations will be summarized with descriptive statistics. The modified Hexsel CSS total score at each post baseline visit will be compared with baseline using paired t-test. Mean difference between baseline and each post baseline visit modified Hexsel CSS total score along with 95% CI for modified Hexsel CSS total score, standard error and corresponding p-value will also be provided. In case normality assumptions are not met then Wilcoxon signed rank test will be used.

**Global Aesthetic Improvement Scale**

For GAIS, the number and proportion of participants with an improvement (participants who experienced “improved”, “much improved”, and “very much improved”) will be presented.

# TABLE OF CONTENTS

1. TITLE PAGE ..... 1
PROTOCOL AUTHORIZATION ..... 3
INVESTIGATOR'S AGREEMENT ..... 4
2. SYNOPSIS ..... 5
3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES ..... 17
4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS ..... 24
5. INTRODUCTION ..... 26
5.1. Overview of CBL-514 ..... 26
5.2. Unmet Medical Need ..... 26
5.3. Summary of Nonclinical and Clinical Studies ..... 27
5.3.1. Nonclinical Studies ..... 27
5.3.2. Clinical Studies ..... 27
5.4. Rationale for the Study ..... 27
5.5. Rationale for Dose Selection ..... 28
5.6. Dosage and Treatment Periods ..... 28
5.7. Participant Population ..... 28
5.8. Ethical Principles ..... 29
6. TRIAL OBJECTIVES AND ENDPOINTS ..... 30
6.1. Objectives ..... 30
6.1.1. Efficacy Objectives ..... 30
6.1.2. Safety and Tolerability Objectives ..... 30
6.2. Endpoints ..... 30
6.2.1. Efficacy Endpoints ..... 30
6.2.2. Safety and Tolerability Endpoints: Stage 1 and Stage 2 ..... 31
7. INVESTIGATIONAL PLAN ..... 32
7.1. Overall Study Design ..... 32
7.2. Number of Participants ..... 37
7.3. Safety Review Committee ..... 37
7.4. Stopping Criteria for Overall Study ..... 38

7.5. Stopping Criteria for Participant....38
7.6. Criteria for Study Termination....38
8. SELECTION AND WITHDRAWAL OF PARTICIPANTS....47
8.1. Participant Inclusion Criteria....47
8.2. Participant Exclusion Criteria....47
8.3. Prohibitions and Restrictions in the Study....49
8.3.1. Medications and Supplements....49
8.3.2. Contraception....50
8.3.3. Fasting....50
8.4. Screen Failures....50
8.5. Participant Replacement....50
8.6. Participant Withdrawal Criteria....50
9. TREATMENT OF PARTICIPANTS....52
9.1. Description of Investigational Product....52
9.1.1. Investigational Product....52
9.1.2. Reference Products....52
9.2. Dosage and Treatment Periods....52
9.3. Concomitant Medications....52
9.4. Treatment Compliance....53
9.5. Protocol Deviations....53
9.6. Blinding....53
10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT....54
10.1. Investigational Product....54
10.2. Investigational Product Packaging and Labeling....54
10.3. Investigational Product Storage....54
10.4. Investigational Product Preparation....54
10.5. Administration....54
10.6. Investigational Product Accountability....54
10.7. Investigational Product Handling and Disposal....55
11. STUDY SCHEDULE....56
11.1. Screening (Day -28 to Day -1)....56
11.2. Treatment Visits....56
11.3. Follow-up Visits....56

11.4. Early Termination Visit .....56
11.5. End of Study (EOS) .....56
12. SAFETY ASSESSMENTS .....57

13. STATISTICS ..... 70
13.1. Sample Size ..... 70
13.2. Analysis Populations ..... 70
13.2.1. Safety Population ..... 70
13.2.2. Intent-to-Treat Population ..... 70
13.2.3. Per-Protocol Population ..... 70
13.3. Statistical Methods ..... 71
13.3.1. Participant Disposition ..... 71
13.3.2. Demographics, Medical History, and Baseline Characteristics ..... 71
13.3.3. Prior and Concomitant Medication ..... 71
13.3.4. Treatment Compliance and Exposure ..... 71
13.4. Safety Analyses ..... 71
13.4.1. Adverse Event ..... 71
13.4.2. Treatment-Emergent Adverse Events of Special Interest ..... 72
13.4.3. Laboratory Evaluations ..... 72
13.4.4. Vital Signs ..... 72
13.4.5. Electrocardiograms ..... 72
13.4.6. Other Safety Assessments ..... 72
13.5. Efficacy Assessments ..... 72
13.5.1. [redacted]
13.5.2. [redacted]
14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS ..... 74
14.1. Study Monitoring ..... 74
14.2. Data Management ..... 74
14.3. Audits and Inspections ..... 75
15. QUALITY CONTROL AND QUALITY ASSURANCE ..... 76
15.1. Compliance with Good Clinical Practice ..... 76
15.2. Archiving and Regulatory Inspection ..... 76
16. ETHICS ..... 77
16.1. Ethics Review ..... 77
16.2. Ethical Conduct of the Study ..... 77
16.3. Written Informed Consent ..... 77
16.4. Data Protection ..... 78

17. DATA HANDLING AND RECORDKEEPING ..... 79
17.1. Inspection of Records ..... 79
17.2. Retention of Records ..... 79
17.3. Liability/Indemnity/Insurance ..... 79
18. PUBLICATION POLICY ..... 80
19. LIST OF REFERENCES ..... 81
20. APPENDICES ..... 82
20.1. Appendix 1: Reference images of treatment area ..... 82
20.2. Appendix 2: Reference List of Prohibited Substances (CYP inhibitors and inducers only) ..... 83
20.3. Appendix 3: Contraceptive Methods ..... 84

# LIST OF TABLES

Table 1: Abbreviations and Specialist Terms ....24
Table 2: Scoring System of Cellulite Severity ....33
Table 3: Dosing Scheme – Stage 1 (note: the concentration of CBL-514 is 5 mg/mL) ....34
Table 4: Dosing Scheme – Stage 2 ....37
Table 5: Schedule of Assessments – Stage 1 ....41
Table 6: Schedule of Assessments – Stage 2 ....44
Table 7: Investigational Product ....52
Table 8: Injection Site Reaction Severity Assessment ....62
Table 9: Criteria for Determination of Relationship to Drug Administration Procedure ....64
Table 10: Reference List of Prohibited Substances (CYP inhibitors and inducers only) ....83

# LIST OF FIGURES

Figure 1: Study Design.....40

# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 1: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| AE | Adverse event |
| AESI | Adverse events of special interest |
| Ag/Ab | Antigen/antibody |
| ATC | Anatomical therapeutic chemical |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Hexsel CSS | Hexsel cellulite severity scale |
| eCRF | Electronic case report form |
| ECG | Electrocardiogram |
| EFP | Edematous fibrosclerotic panniculopathy |
| EOS | End of study |
| ET | Early termination |
| FDA | United States Food and Drug Administration |
| FIH | First in human |
| FSH | Follicle-stimulating hormone |
| GAIS | Global Aesthetic Improvement Scale |
| GCP | Good Clinical Practice |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Council for Harmonization |
| IP | Investigational product |
| IRB | Institutional Regulatory Board |
| ISR | Injection site reaction |
| ITT | Intent-to-treat |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MM | Medical Monitor |
| NCI | National Cancer Institute |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| NOAEL | No observed adverse effect level |
| NSAID | Nonsteroidal anti-inflammatory drug |
| OTC | Over-the-counter |
| PI | Principal Investigator |
| PP | Per protocol |
| PT | Preferred term |
| PV | Pharmacovigilance |
| SAD | Single ascending dose |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SOC | System organ class |
| SRC | Safety Review Committee |
| TEAE | Treatment-emergent adverse event |
| ULN | Upper limit of normal |
| WHO | World Health Organization |
| WOCBP | Woman of childbearing potential |

# 5. INTRODUCTION

## 5.1. Overview of CBL-514

CBL-514 is an injection lipolysis product developed by Caliway which has shown promising efficacy and safety profiles in prior research for the proposed indication in promoting adipose cell apoptosis. The active pharmaceutical ingredient (CBL-514-API) consists of trans-resveratrol (CAS number: 501-36-0) and curcumin (CAS number: 458-37-7). The complete details of CBL-514 are described in detail in the Investigator's Brochure (IB) (Version 1.0, dated 17 June 2022 ).

## 5.2. Unmet Medical Need

Cellulite is a change to the surface of the skin that commonly occurs in women and is rare in men, with the exception of androgen deficiency. Cellulite is characterized by the nonpathological appearance of dimpled skin surface (likened to orange peel, cottage cheese, or mattress appearance) which occurs on the thighs and buttocks and less commonly on the breasts, abdomen and arms. It can be accompanied by the feeling of heaviness in the limbs, pain, hypoesthesia, or localized cold feeling (Rossi and Katz 2014).

The etiology of cellulite has been attributed to hormonal, circulatory, structural, and inflammatory factors. Cellulite appears to be the result of localized adipose deposits and edema within the subcutaneous tissue. Bands of connective tissue, or septa, are oriented longitudinally, from deep fascia to the dermis. These fibrous bands segregate fat into channels. As the fat lobes expand with increasing adipocyte size, they push up against the skin while the fibrous septa pull down and the channels project superficially creating an undulating skin surface or puckered appearance of the skin (Hexsel and Soirefmann 2011). As men have a thicker dermis and a random septa connection pattern, rather than right angled, pattern of septa connections between the dermis and the deep fascia, these structural variations are likely involved in the lower incidence of cellulite in men.

Treatments for cellulite typically aim to change the structure of the dermis and connective tissue and/or improve circulation. These therapeutic approaches include 1) noninvasive devices including mechanical massage or suction, with or without light, laser or radiofrequency sources or ultrasound 2) invasive techniques including liposuction, excision lifts such as a thigh lift and subcision (mechanical cutting of the retracting hypertrophic septa) 3) injectables such as Qwo® , a phosphatidyl choline mesotherapy and 4) topical application of crèmes etc. including caffeine and other methylxanthines, yohimbine, and retinol.

Most of the treatments have mild, short term improvements in the appearance of cellulite, but are not sustainable. For example, the United States Food and Drug Administration (FDA) approved treatment options for cellulite include Qwo, CellfinaSystem, Cynosure CellulazeLaser, and Rapid Acoustic Pulse Device. The rationale of these treatments is to break up the fibrous structure that secure the fat protrusion and hence to free the skin surface. Although the skin appear even and smooth, it does not alter the fat pockets that push against the dermis. The broken strands eventually reconnect in the same fashion and cause fat protrusion which is cellulite again (DiBernardo 2011). Due to the mechanism of action, these treatments may cause moderate to

severe administration site bruising in a profound area to treatment site (Hexsel and Milano 2000).

While there are many therapeutic options due to the number of approaches, there is no definitive therapy and cellulite remains a condition elusive to treatment.

## 5.3. Summary of Nonclinical and Clinical Studies

### 5.3.1. Nonclinical Studies

CBL-514 has undergone an extensive nonclinical safety evaluation. All nonclinical studies conducted for CBL-514 are described in detail in the Investigator's Brochure (Version 1.0, dated 17 June 2022).

### 5.3.2. Clinical Studies

A first in human (FIH) Phase 1/2a (protocol number CBL-16001) study has been conducted to evaluate the safety, tolerability (Phase 1 study), and preliminary efficacy of CBL-514 injection for reducing convexity or fullness of abdominal subcutaneous fat (Phase 2a study). The exposure dose of CBL-514 dose in this FIH Phase 1/2a (protocol number CBL-16001), ranged from 2 mg to 320 mg in the Phase 1 study and from 180 to 300 mg in the Phase 2a study. The summation of the FIH Phase 1/2a (protocol number CBL-16001), demonstrated that CBL-514 was safe and well tolerated when administered via injection into the abdominal subcutaneous adipose layer and that CBL-514 treatment is associated with clinically meaningful and statistically significant improvement in abdominal subcutaneous fat volume as well as fat thickness.

There are 2 Phase 2 studies are ongoing to evaluate the efficacy, safety, and pharmacodynamic profile of CBL-514 at a higher dose. One study (protocol number CBL-0202) aims to evaluate the safety of the maximum dose use of CBL-514 via dose escalation up to 800 mg in the first stage. The second stage of the study will evaluate the efficacy and safety of multiple doses of CBL-514 up to 600 mg. Another Phase 2 study (protocol number CBL-0203) will assess the pharmacodynamic profile of the maximum dose of CBL-514 (i.e. 800 mg).

## 5.4. Rationale for the Study

The FIH Phase 1/2a (protocol number CBL-16001) study had a good safety and tolerability profile to a dose exposure of 320 mg and showed good efficacy to a dose exposure of 300 mg in humans. The overall conclusion for the FIH study was that CBL-514 injection at multiple doses up to 300 mg had no safety concerns and was well tolerated in adult subjects, and showed statistically significant decreases in fat volume and fat thickness compared to baseline.

This is a 2-stage adaptive design, Phase 2a open label study to evaluate the safety, tolerability, and efficacy of CBL-514 injection for the treatment of edematous fibrosclerotic panniculopathy (EFP); cellulite. The results from a clinical study conducted to evaluate the efficacy CBL-514 abdominal subcutaneous fat volume as well as fat thickness (FIH Phase 1/2a [protocol number CBL-16001]), suggest that subcutaneous administration of CBL-514 may be effective in the improvement of EFP measured by cellulite in humans. The pharmacological studies conducted by Caliway Biopharmaceuticals support the intended clinical dose and route of administration of the planned Phase 2 study (refer to further details in IB).

## 5.5. Rationale for Dose Selection

The selection of dosing for Stage 1 and Stage 2 of this study is based on the safety and efficacy results of the FIH Phase 1/2a (protocol number CBL-16001), which demonstrated that CBL-514 injection at multiple doses up to 300 mg with unit dose 2.0 mg/cm$^2$ had no safety concerns and demonstrated good efficacy in reducing the abdominal fat volume and thickness by inducing adipocyte apoptosis.

## 5.6. Dosage and Treatment Periods

This is a 2-stage adaptive design, Phase 2a study to evaluate the safety, tolerability, and efficacy of CBL-514 injection for the treatment of EFP; cellulite. CBL-514 will be injected on the posterolateral thigh, preferably on the lateral side, to treat the EFP (See Section 20.1 Appendix 1). This Phase 2a study has an integrated design consisting of a single ascending dose (SAD) part in Stage 1 followed by a single-arm design in Stage 2. Participants that enroll in Stage 1 of the study will not be eligible to take part in Stage 2 of the study.

A total of up to 32 participants (n = 12 in Stage 1; n = 20 in Stage 2) with moderate or severe EFP will be enrolled. Cellulite improvement will be evaluated by the Investigator (or designee) by using a modified Hexsel CSS. The GAIS assessment will be reported by the clinician and participant, respectively, to evaluate the respond rate of cellulite improvement.

**Stage 1 (single dose escalation, open label)**

Each participant will participate in Stage 1 of the study for approximately 5 weeks, including Screening (Visit 1), baseline visit on Day 1 (Visit 2), and 3 follow-up visits at Week 1 (Visit 3), Week 2 (Visit 4), and Week 4 (Visit 5), per the Schedule of Assessments (Table 5). Participants will receive 1 course of allocated CBL-514 dose administered by subcutaneous injection on both sides of the posterolateral thighs on Day 1 (Visit 2). The dosing scheme for Stage 1 is presented in Table 3.

**Stage 2 (up to 2 courses, single arm study)**

Each participant will participate in Stage 2 of the study for approximately 20 weeks. The study periods are set out as follows: Screening (Visit 1), admission/first treatment visit on Day 1 (Visit 2), second treatment visit (Visit 3), and 2 follow-up visits (Visit 4 and Visit 5) per the Schedule of Assessments (Table 6). Each participant will receive up to 2 courses of CBL-514 administered by subcutaneous injection on both posterolateral thighs. The IP will be administered on Visit 2 (Day 1) and then at Visit 3 (Visit 2 + 4 weeks [± 7 days]) following the first dose. The dosing scheme for Stage 2 is presented in Table 4.

Duration of study participation is defined as the period between the day the participant provides written consent and until all study required examinations have been completed.

## 5.7. Participant Population

The study will be conducted in healthy female volunteers aged 18 to 64 years (inclusive at the time of informed consent).

Women of childbearing potential (WOCBP) will be included and are subject to contraceptive requirements during the study from Screening until study completion, including the follow-up period, and for at least 90 days after the last dose of the investigational product (IP) (see Section 8.2). Women of childbearing potential must demonstrate negative pregnancy testing at Screening

and before administration of the IP. This is in line with regulatory Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (FDA 2006).

## 5.8. Ethical Principles

This study will be conducted in accordance with the principles of the current Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and applicable local regulatory requirements. The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice (GCP) ICH E6 (R2). This study will be conducted under a protocol reviewed and approved by an Institutional Regulatory Board (IRB) and investigations will be undertaken by scientifically and medically qualified persons; where the benefits of the study are in proportion to the risks.

# 6. TRIAL OBJECTIVES AND ENDPOINTS

## 6.1. Objectives

### 6.1.1. Efficacy Objectives

Stage 1:

Primary efficacy:

- To evaluate the improvement of EFP measured by cellulite severity scale from baseline following administration of 1 course of CBL-514.

Stage 2:

Primary efficacy:

- To evaluate the improvement of EFP measured by cellulite severity scale from baseline following administration of at least 1 course of CBL-514.

Secondary efficacy:

- To evaluate the response rate of EFP improvement by Global Aesthetic Improvement Scale (GAIS) reported by the clinician and participant, respectively, following administration of at least 1course of CBL-514.

### 6.1.2. Safety and Tolerability Objectives

Stage 1:

- To evaluate safety and tolerability following administration of 1 course of CBL-514.

Stage 2:

- To evaluate safety and tolerability following administration of at least 1 course of CBL-514.

## 6.2. Endpoints

### 6.2.1. Efficacy Endpoints

Stage 1:

Primary efficacy

- Change in total scores from baseline according to the modified Hexsel cellulite severity scale (CSS) at V4 and V5.

Secondary efficacy:

- Percentage of participants' thighs that achieve at least 1-level severity improvement determined by the total scores of modified Hexsel CSS at V4 and V5 compared to baseline.

Stage 2:

Primary efficacy:

- Change in total scores according to the modified Hexsel CSS at V4.

Secondary efficacy:

- Percentage of participants' thighs with at least 1-level severity improvement determined by the total scores of modified Hexsel CSS at V4 and V5 compared to baseline.
- Change in total scores according to the modified Hexsel CSS at V5.
- Percentage of participants' thighs with achieve at least 2-score improvement in modified Hexsel CSS at V4 and V5.
- Percentage of participants with improvement in GAIS assessed by the clinician and participant, respectively.

### 6.2.2. Safety and Tolerability Endpoints: <u>Stage 1 and Stage 2</u>

- Safety and tolerability endpoints will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Assessments will be inclusive of:
  - adverse events and treatment-emergent adverse events,
  - adverse events and treatment-emergent adverse events at the injection site(s),
  - adverse events and treatment-emergent adverse events related to the IP,
  - adverse events of special interest,
  - clinically significant laboratory findings including hematology, biochemistry, coagulation, and urinalysis tests,
  - clinically significant abnormalities in physical examination, 12-lead electrocardiogram parameters, and vital signs, and
  - use of concomitant medications to treat treatment-emergent adverse events (TEAEs).

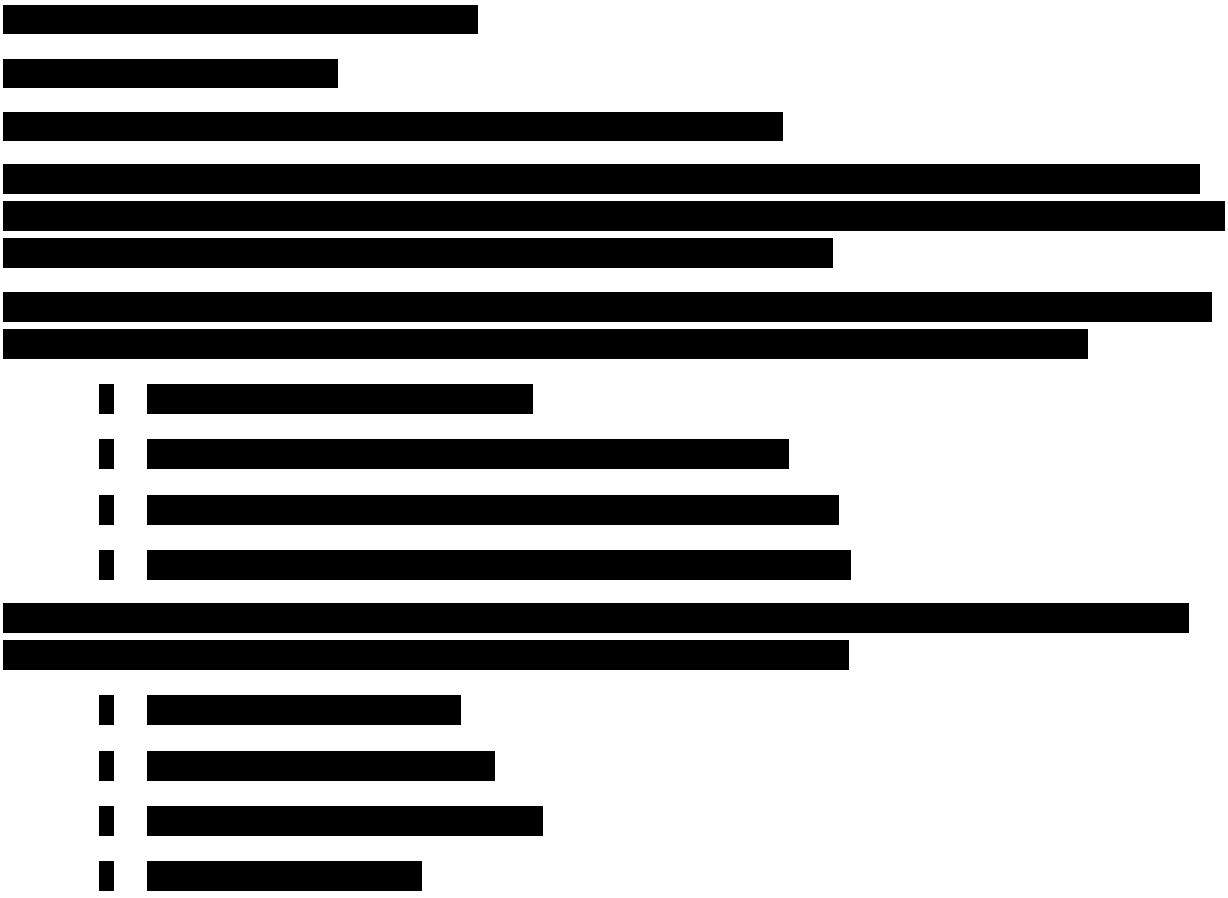
# 7. INVESTIGATIONAL PLAN

## 7.1. Overall Study Design

This is a 2-stage adaptive design, Phase 2a study to evaluate the safety, tolerability, and efficacy of CBL-514 injection for the treatment of EFP; cellulite. CBL-514 will be injected on the posterolateral thigh, preferably on the lateral side, to treat the EFP (See Section 20.1 Appendix 1). This Phase 2a study has an integrated design consisting of a SAD part in Stage 1 followed by a single-arm design in Stage 2. Participants that enroll in Stage 1 of the study will not be eligible to take part in Stage 2 of the study.

A total of up to 32 participants (n = 12 in Stage 1; n = 20 in Stage 2) with moderate or severe EFP will be enrolled. Cellulite improvement will be evaluated by the Investigator (or designee) by using a modified Hexsel CSS (Hexsel and Dal'Forno 2009). The GAIS assessment will be reported by the clinician and participant, respectively, to evaluate the respond rate of cellulite improvement.

Hexsel CSS is composed of 5 key morphological aspects which includes (A) the number of depressions, (B) depth of depressions, (C) clinical appearance of evident raised lesions, (D) the presence of flaccidity, and (E) the classification scale originally described by Nürnberger and Müller (Nurnberg and Muller 1978). The severity of cellulite in this study will be assessed using a modified Hexsel CSS. This modified Hexsel CSS is based on the following descriptors:



[redacted]

The severity level of cellulite will be scored as mild, moderate, or severe which will be determined by the total scores obtained from items A to C as illustrated in Table 2

**Table 2: Scoring System of Cellulite Severity**

| Cellulite Severity Total Score | Cellulite Severity Level |
|---|---|
| 0 | None |
| 1 to 3 | Mild |
| 4 to 6 | Moderate |
| 7 to 9 | Severe |

The GAIS is a 5-point scale rating aesthetic improvement in appearance, compared with pretreatment, as judged by the Investigator. The rating categories are 'worse', 'no change', 'improved', 'much improved', and 'very much improved'

A schematic of the study design for Stage 1 and Stage 2 is provided in Figure 1.

Study visits and assessments for will occur as delineated in the Schedule of Assessments (Table 5 [Stage 1] and Table 6 [Stage 2]).

The dosing scheme for Stage 1 is presented in Table 3 and the dosing scheme for Stage 2 is presented in Table 4.

Participants will undergo a Screening period, beginning up to 28 days before the first dose of the IP, and will be required to sign an informed consent form (ICF) before undertaking any study-specific procedures or assessments. Participants who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study.

**Stage 1 (single dose escalation, open label)**

The Stage 1 will include a total of 12 participants enrolled in 3 sequential escalating CBL-514 dose groups: 1.0 mg/cm$^2$, 1.5 mg/cm$^2$, and 2.0 mg/cm$^2$. The groups will be open label and each group will enroll 4 participants.

Eligible participants will be sequentially assigned to receive once course of allocated CBL-514 dose administered by subcutaneous injection on both sides of the posterolateral thighs on Day 1. When the IP is administered, the number of injections per posterolateral side of the thigh does not need to be distributed equally. The dosing scheme is presented in Table 3.

**Table 3: Dosing Scheme – Stage 1 (note: the concentration of CBL-514 is [redacted])**

| Group | Dose Level (mg /cm$^2$) | Injection Volume per 1 cm$^2$ Grid | Administration for 1 Course | | |
|---|---|---|---|---|---|
| | | | Total No. of Injections | Total Injection Volume (mL) | CBL-514 (mg) |
| 1 | 1.0 | 0.2 mL | 40 | 8 | [redacted] |
| 2 | 1.5 | 0.3 mL | 40 | 12 | [redacted] |
| 3 | 2.0 | 0.4 mL | 40 | 16 | [redacted] |

[redacted] A detailed description for how the treatment area is to be demarcated will be provided in the IP administration manual.

Prior to IP administration, cold compress will be applied to the treatment area. The usage of topical anesthetic cream (5% to 10% lidocaine) prior to administration of the IP will be evaluated before dose escalation to Group 2 and/or Group 3, and will depend on the participant's tolerance to injection site pain during IP administration. The same procedure prior to the IP administration will be adopted in each group, respectively. After the administration, participants will remain in the research unit for observation and until all planned assessments for the visit are completed. Prior to the discharge after treatment, interventional or prophylactic medications (such as analgesics for injection site pain) may be provided to participants at the discretion of the Investigator. Participants will visit the site at Week 1/Visit 3, Week 2/Visit 4, and Week 4/Visit 5 post dose for safety and efficacy follow-up assessments.

An early termination (ET) visit will be planned if a participant who has received treatment withdraws from the study early. The ET visit will follow the procedures of Stage 1 Week 1/Visit 3.

To accompany follow-up assessments, a participant diary will be provided to each participant to record any injection site reactions/changes to the injection site/s or any discomforts post Day 1 (post IP administration) until Visit 5 (EOS). Participants will be instructed to bring the participant diary with them for the designated visits to the clinic.

During Stage 1 of the study, the safety review meeting will be held after 4 participants in a dose group complete the Week 1 visit. The Safety Review Committee (SRC) will review all reported adverse events (AEs), adverse events of special interest (AESIs), and the results of safety assessments of all participants from each dose group. Based upon review of available safety and tolerability data from each preceding dose group, the SRC will make a decision on proceeding to the next dose group.

The safety and tolerability data from Stage 1 will be reviewed by the SRC before commencement of Stage 2. The SRC will decide a recommended dose for Stage 2 of the study. The protocol including the final decision of the Stage 2 dose will be submitted to the IRB for review and approval before proceeding to Stage 2 of the study.

**Stage 2 (up to 2 courses, single arm study)**

Stage 2 of the study will be initiated after IRB review of the protocol which includes the conformed Stage 2 dose. Stage 2 will be conducted as a single arm study with one selected CBL-514 dose. The unit dose of CBL-514 used in the Stage 2 will be no higher than the highest safe unit dose from Stage 1.

In Stage 2 of the study, up to 20 participants will be enrolled. Participants that enroll in Stage 1 of the study will not be eligible to take part in Stage 2 of the study. Each participant will receive up to 2 courses of CBL-514 administered by subcutaneous injection on both posterolateral thighs. The first dose will be administered at Visit 2 on Day 1 and the second dose will be administered at Visit 3 (Visit 2 + 4 weeks [± 7 days]) following the first dose.

The area which is to be treated will be assessed at Screening by the Investigator (or designee). This will include an evaluation of the enrollment criteria for the cellulite severity score and the overall area (coverage) of cellulite. Based on this assessment, the Investigator will make a determination with regards to the injection number for the participant. [redacted] A detailed description for how the treatment area is to be demarcated will be provided in the IP administration manual.

Prior to administering the second treatment with CBL-514 at Visit 3 the Investigator (or designee) will evaluate the severity of EFP assessed by the modified Hexsel CSS items (A), (B), and (C). If the cellulite severity level at the original treatment site of both thigh are assessed as either Mild or None according to the modified Hexsel CSS assessment, the second treatment of CBL-514 will not be administered at Visit 3. Instead these participants will proceed to the follow-up assessments in accordance with Visit 4 procedures and for these participants the second follow-up will be performed at Visit 5, scheduled for 12 weeks (± 7 days) post Day 1 in accordance with Visit 5 procedures. On the other hand, if only one thigh is assessed as either Mild or None according to the modified Hexsel CSS assessment, the second treatment of CBL-514 can still be administrated to the other thigh and the injection number should between 20 to 80.

If the participants complete 2 treatment visits, the first follow-up Visit 4 will be performed 4 weeks (± 7 days) post Visit 3 and the second follow-up Visit 5 will be performed 12 weeks (± 7 days) post Visit 3.

An ET visit will be planned if a participant who has received treatment withdraws from the study early. The ET visit will follow the procedures of Visit 4. All study assessments for all visits and follow-up will be conducted as per the Schedule of Assessments.

To accompany follow-up assessments, a participant diary will be provided to each participant to record any injection site reactions/changes to the injection site/s or any discomforts post Day 1 (post IP administration) until Visit 5 (EOS) or when all injection site reactions have resolved or stabilized. Participants will be instructed to bring the participant diary with them for the designated visits to the clinic.

At least 40 injections and up to 160 injections in total will be administered to both posterolateral thighs per treatment. When the IP is administered, the number of injections per posterolateral side of the thigh does not need to be distributed equally. The dosing scheme is presented in Table 4.

**Table 4: Dosing Scheme – Stage 2**

| Group | Dose Level (mg /cm$^2$) | Injection Volume per 1 cm$^2$ Grid | Administration per Treatment (minimum / maximum) | | |
|---|---|---|---|---|---|
| | | | Total No. of Injections | Total Injection Volume (mL) | CBL-514 (mg) |
| 1 | 2.0 | 0.4 mL | 40 / 160 | 16 / 64 | [redacted] |

Prior to IP administration, cold compress will be applied to the treatment area. The usage of topical anesthetic cream (5% to 10% lidocaine) prior to administration of the IP will be evaluated before a participant receives the second treatment, and will depend on the participant's tolerance to injection site pain during the first treatment. Participants will remain in the research unit for observation after the administration of the IP, and until all planned assessments for the visits are completed. Prior to the discharge after treatment, interventional or prophylactic medications (such as analgesics for injection site pain) may be provided to participants at the discretion of the Investigator.

During Stage 2 of the study, if a participant experiences an AESI following the first administration of the IP, the Investigator (or designee) will report the event to Sponsor and Medical Monitor (MM) within 24 hours upon the event being noticed by the Investigator or designee. The SRC will review the safety data of the participant and decide whether the participant experiencing the AESI should proceed with the second course of CBL-514.

## 7.2. Number of Participants

A total of 32 participants are planned to be enrolled for the 2-stage study.

- Stage 1 will enroll 12 participants in 3 sequential dose groups.
- Stage 2 will enroll up to 20 participants in a single dose group.

## 7.3. Safety Review Committee

Oversight will be provided by an SRC comprised of the Investigator, the Sponsor's representative, and an independent MM. The SRC will be established prior to Screening and the details of which will be set out in an SRC Charter.

The SRC will have overall responsibility for any safety and tolerability decisions for the following scenarios:

- Escalation to next dose level in Stage 1 of the study
- Review of safety data of a participant who experiences an AESI prior to proceeding to the second course of CBL-514 treatment in Stage 2 of the study
- Recommendations for any event meeting Stopping Criteria (see Section 7.4 and Section 7.5)

If at any time the study is terminated, a written statement fully documenting the reasons for termination will be provided to the relevant IRB.

## 7.4. Stopping Criteria for Overall Study

Administration of IP may be paused, and all participants will not receive further treatments, until a consultation has taken place between the Investigator, the independent MM, and the Sponsor representative under the following circumstances:

1. any participant experiences an adverse event as Grade 3 or higher (as defined in the NCI-CTCAE version 5.0) for a cardiovascular, renal, or hepatic event considered to be at least possibly related to IP
2. except for cardiovascular, renal, or hepatic events specified in Criterion #1, any participant experiences a Grade 4 or higher clinical or laboratory abnormality (as defined in the NCI-CTCAE version 5.0) considered to be at least possibly related to IP
3. any participant experiences a serious adverse event (SAE) that is considered to be at least possibly related to IP
4. an AE or group of AEs that singularly or in aggregate suggests to the Investigator or Sponsor that the IP is poorly tolerated and further treatment per protocol (PP) may not be safe.

If any one participant meets a stopping criterion for overall study, the study will be suspended from continuing treatment visits for all participants. Participants should remain in the study and be followed until the AE resolves or stabilizes.

If any of these criteria occur, the SRC review will take place as soon as possible to evaluate the event and decide whether the treatment can continue for the rest of the participants.

## 7.5. Stopping Criteria for Participant

If a participant experiences any of following circumstances, the participant should not receive additional IP administration. If any of these criteria occur, the event will be reported to the Sponsor and MM within 24 hours upon noticed by the PI or delegates.

1. A Grade 2 or higher grade adverse event (as defined in the NCI-CTCAE version 5.0) for bone marrow or cardiovascular event
2. Except for bone marrow and cardiovascular event specified in Criterion #1 and expected injection site reactions (refer to Investigator Brochure), a Grade 3 or higher grade adverse event (as defined in the NCI-CTCAE version 5.0).

## 7.6. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study. This may be determined by the Sponsor, the Investigator, the IRB, or regulatory authorities.
- The study is terminated by the Sponsor for administrative reasons.

The Sponsor, Investigator, and the IRB reserve the right to terminate or suspend the study at any time; however, this should be discussed between the relevant parties beforehand and the reason for such decision recorded. Should this occur, all data available will also be recorded in the electronic Case Report Forms (eCRFs). If the Sponsor, the IRB, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor. The procedure will be followed by the investigational site during termination or study suspension.

The Investigator should notify the relevant IRB and/or regulatory authority in writing of the study's completion or early discontinuation.

**Figure 1: Study Design**

**Study Timeline: Stage 1**

**Study Timeline: Stage 2**

Abbreviations: ET = Early termination; EOS = End of study.

**Table 5: Schedule of Assessments – Stage 1**

| [redacted] | [redacted] | [redacted] | [redacted] | | |
|---|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | | | | |
| [redacted] | [redacted] | [redacted] | | | |
| [redacted] | [redacted] | | | | |
| [redacted] | | | | | |
| [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | | | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | [redacted] | [redacted] | | |
| [redacted] | [redacted] | | | | |
| [redacted] | [redacted] | | | | |
| [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | | | |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

[redacted]

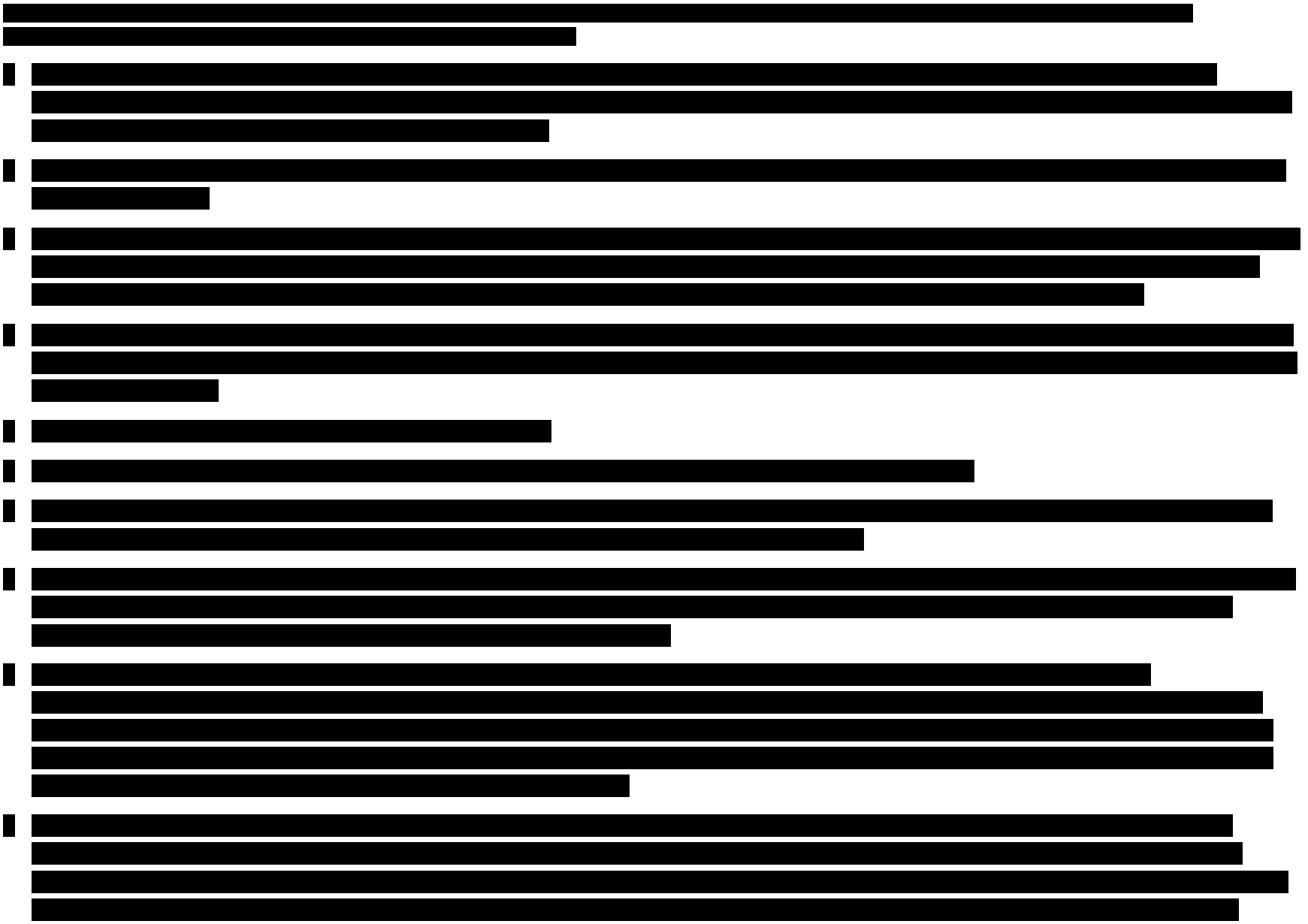


**Table 6: Schedule of Assessments – Stage 2**

9 Eight-hour fasting blood tests will be performed pre-dose at treatment visits. Blood assessments will be conducted within 3 days or at treatment/follow-up visit. Blood tests include biochemistry, hematology, and coagulation. Biochemistry assessments include albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), sodium (Na), potassium (K), chloride (Cl), triglyceride, total cholesterol, total bilirubin (TBIL), Gamma-glutamyl transferase (GGT), urea, creatinine, estimated glomerular filtration rate (eGFR), hemoglobin A1c (HbA1c), and fasting blood sugar (FBS). Hematological assessments include hemoglobin (Hb), hematocrit (Hct), RBC count, mean corpuscular volume, leukocyte/white blood cell (WBC) count with absolute differential count, and platelet count. Coagulation assessments include activated partial thromboplastin time (aPTT), prothrombin time, and international normalized ratio (INR).

10 Urinary samples for qualitative dipstick test will be collected. Assessment will be performed pre-dose at treatment visits and will be collected within 3 days or at treatment/follow-up visit. If abnormality is noted for protein, blood, nitrite, or leukocyte esterase (and at the discretion of the Investigator, or designee) a microscopic examination of RBC, WBC, bacteria, and casts will be performed.

11 Serum β-hCG test will be taken for WOCBP at Screening visit only. Urine qualitative hCG strip test will be taken for WOCBP at other scheduled visits. If the urine qualitative hCG strip test is positive, the result will be confirmed by a serum β-hCG test. If IP dose is within 7 days of Screening pregnancy test, pregnancy test on Day 1 will not be necessary to assess.

12 FSH test is required for females who are postmenopausal at the Screening visit.

13 Virology tests include HIV/HBV/HCV infection test. Active HIV infection is detected by a positive HIV antigen/antibody (Ag/Ab) combination test; HBV by a positive HBsAg test; and HCV by a positive anti-HCV antibody test.

14 Photography will be performed prior to and post the administration of the IP at treatment visits and at follow-up visits to record the appearance of cellulite around treatment area. Uniformed camera will be used. Details of photography requirements are outlined in the photography manual.

15 If treatment is not administered at Visit 3, the schedule of follow-up visits should be based on the Visit 2 date, where the last treatment is performed.

16 All AEs will be followed until resolution, or until the event is considered stable.

17 On the days when participants are being administered the IP, AEs for ISRs will be assessed prior to and post the administration of the IP.

18 At Visit 5, only collect the information if a medication is related to AEs.

# 8. SELECTION AND WITHDRAWAL OF PARTICIPANTS

## 8.1. Participant Inclusion Criteria

To be eligible to enter the study, participants ***must meet all*** of the following inclusion criteria:

1. Female aged 18 years to 64 years old (at Screening), inclusive.
2. Have a BMI > 18.5 and < 35 kg/m$^2$ and body weight ≥ 50 kg at Screening and Day 1.
3. The participant has both sides of posterolateral thighs assessed according to the modified Hexsel CSS (A) number of evident depressions, (B) depression depth scale, and (C) morphological appearance of skin surface alterations. On assessment by modified Hexsel CSS, the participant scores at least 4 and no greater than 8 at Screening and Day 1. The total score must contain:
   a. Hexsel CSS item (A) 'number of evident depressions' score of ≥ 1,
   b. Hexsel CSS item (B) 'depth of depressions' score of ≥ 1.
4. Participant has a stable lifestyle (e.g., exercise, eating patterns, and smoking habit) per participant report for at least 3 months before Screening and during the study.
5. Voluntarily signs the informed consent form and, in the opinion of the Investigator or delegate, is physically and mentally capable of participating in the study, and willing to adhere to study procedures.

## 8.2. Participant Exclusion Criteria

A participant who meets ***any*** of the following exclusion criteria must be excluded from the study:

1. Female participant of childbearing potential who is not willing to commit to an acceptable contraceptive regimen with her partner from the time of Screening and throughout study participation until 90 days after the last IP dose, or who is currently pregnant or lactating. Complete details of acceptable contraception are provided in Section 20.3 Appendix 3.

   Note: females who are not of childbearing potential are not required to use contraception. Females not of childbearing potential are defined as those who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are postmenopausal (defined as aged at least 50 years old with ≥ 12 months of amenorrhea and a follicle-stimulating hormone (FSH) level > 30 IU/L at Screening).
2. Participant diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation within 14 days prior to the IP administration.
3. Participant has hemoglobin A1c (HbA1c) ≥ 9%, delayed wound healing, or any diabetic risks which, in the opinion of the Investigator (or designee) is inappropriate to participate in the study.

4. Participant has a clinically significant cardiovascular disease and abnormal findings in electrocardiogram (ECG) at Investigator's (or designee's) discretion.
5. Participant with active or prior history of malignancies within 5 years before Screening or being assessed for a possible malignancy. Except adequately treated basal cell carcinoma of the skin and in situ squamous cell carcinoma of the skin would be eligible as per Investigator's (or designee's) discretion.
6. Participant with a history of human immunodeficiency virus (HIV)-1 infection, or participants with active HIV infection at Screening with a positive HIV antigen/antibody (Ag/Ab) combination test.
7. Participant with a history of trypanophobia, the extreme fear of medical procedures involving injections or needles, or who experiences vasovagal syncope and passes out at the sight of blood or a needle.
8. Participant with any hepatic medical condition that, in the opinion of the Investigator (or designee), would interfere with assessment of safety or efficacy or compromise the participant's ability to undergo study procedures or provide informed consent.
9. Participant who has a recent history of major depression, anxiety, or other psychiatric disease requiring treatment with prescription medication within 6 months prior to Screening.
10. Participant has abnormal skin or local skin conditions at the treatment area, which in the opinion of the Investigator (or designee), is inappropriate to participate in the study. This includes but is not limited to any of the following:
    a. skin manifestations of a systemic disease
    b. any abnormality of the skin or soft tissues on the anticipated treatment area
    c. skin laxity on treatment area when the participant is in the standing position
    d. sensory loss or dysesthesia in the area to be treated
    e. evidence of any cause of enlargement in the area to be treated other than localized subcutaneous fat
    f. tattoos on the area to be treated
    g. participant with a propensity for keloid or hypertrophic scarring.
11. Participant who has had the following surgical or aesthetic procedures:
    a. liposuction, cryolipolysis, ultrasonic lipolysis, low level laser therapy (LLLT), or lipolysis injection to the region to be treated before Screening
    b. medical device, injection (including but not limited to collagenase clostridium histolyticum injections and collagen stimulating injections), over-the-counter (OTC) cosmetic cream, or cosmetic program to prevent or mitigate EFP to the region to be treated within 12 months before Screening and throughout study participation
    c. massage to the region to be treated within 2 weeks before Screening and throughout study participation.
12. Participant is undergoing chronic steroid or immunosuppressive therapy, except for asthma inhaler or topical steroids for skin conditions if the medications are not used on the treatment area.

13. Participating is requiring continual use of the following therapeutic agents during the study: terfenadine, buspirone, fexofenadine, any medication that is known to strongly inhibit or induce CYP enzymes, sensitive CYP substrates, or drugs with narrow therapeutic index, which in the opinion of the Investigator (or designee), may affect the evaluation of the IP or place the participant at undue risk.

    If a participant needs to use the above-mentioned therapeutic agents during the study for any reason, these therapeutic agents should not be used at least for 2 days before dosing and until 1 day after dosing.

14. Participant receives nonsteroidal anti-inflammatory drug (NSAID) including aspirin within 14 days prior to the IP administration.
15. Participant is unable to receive topical anesthesia (e.g., history of hypersensitivity to lidocaine).
16. Participant with known allergies or sensitivities to the IP or its components.
17. Participant with liver cirrhosis or with inadequate liver function at Screening defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALKP), total bilirubin (TBIL), or gamma-glutamyl transferase (GGT) > 3.0 × upper limit of normal (ULN).
18. Participant with any renal impairment, defined as abnormal serum creatinine, and urea > 1.5 × ULN or estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 $m^2$. Participants who are currently on dialysis should be excluded.

    Participants with an eGFR ≥ 60 and < 90 mL/min/1.73 $m^2$ at Screening should be evaluated by the Investigator to exclude pre-existing renal disease or associated dysfunction. If mild decrease in eGFR is assessed by the Investigator as not clinically significant or not related to dysfunction, the participants may be eligible upon the Investigator's assessment.

19. Use of other IP or device within 4 weeks prior to Screening.

## 8.3. Prohibitions and Restrictions in the Study

### 8.3.1. Medications and Supplements

Participants should be advised not to take any prescription and OTC medications without consulting the Principal Investigator (PI). Throughout the study (i.e., from the Screening visit to the EOS/ET visit), the use of the following medications is prohibited:

a. Anticoagulant/antiplatelet therapy or medications that inhibit coagulation or platelet aggregation within 14 days prior to IP administration;
b. Any cosmetic or interventional surgical procedures on the area to be treated with the IP;
c. Terfenadine (Teldane), buspirone (Buspar), fexofenadine (Fexotabs, Tefodine, Telfast, Xergic, Allegra, etc.), any medication that is known to strongly inhibit or induce CYP enzymes, sensitive CYP substrates (see Section 20.2: Appendix 2), or drugs with a narrow therapeutic index, that in the opinion of the PI may affect evaluation of the study product or place the participant at undue risk (Note: If a

participant requires the above-mentioned therapeutic agents during the study for any reason, they should not be used at least for 2 days prior to dosing and until 1 day post dose);

d. NSAIDs including aspirin within 14 days prior to IP administration;
e. Chronic steroid or immunosuppressive therapy that cause infection or immunodeficiency;
f. Use of other investigational drug or device within 4 weeks prior to Screening.

### 8.3.2. Contraception

Complete details of acceptable contraception are provided in Section 20.3: Appendix 3.

### 8.3.3. Fasting

Pre-dose blood tests will be performed under fasting conditions (8 hours fasting) as delineated in the Schedule of Assessments (Table 5 and Table 6).

## 8.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to be recorded to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes screen failure details, eligibility criteria, and any SAE(s). Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once after the initial screening. Re-screening will be allowed within the recruitment period for the study. Re-screened participants should be assigned a new participant number.

## 8.5. Participant Replacement

Participants who are enrolled but who do not receive any dose of the IP will be replaced and the replacement participants will be assigned the same treatment sequence as the participants they are replacing. Participants who discontinue the study prior to completion of dosing may be replaced (at the discretion of the Sponsor in communication with the Investigator).

## 8.6. Participant Withdrawal Criteria

Participants may withdraw their consent to participate in the study at any time. If a participant withdraws consent, the date and reason for consent withdrawal should be documented. Participants will be encouraged to remain in the study to complete all necessary assessments and until the Investigator deems that it is safe to be withdrawn from the study. Participant data will be included in the analysis up to the date of the withdrawal of consent.

A participant must be removed from the study at any time, if any of the following criteria are met:

- participant withdraws consent,
- participant has body weight change $\geq$ 3kg compared to Day 1 body weight during the whole study period,

- participant has body weight change $\geq$ 3kg during the follow-up period compared to the body weight from the last treatment visit,
- any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the participant continuing on the study.

A clear and concise reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

In accordance with applicable regulations, a participant has the right to withdraw from the study, at any time and for any reason, without prejudice to future medical care.

If a participant is withdrawn because of an AE, the Investigator must arrange for the participant to have appropriate follow-up care until the AE is resolved or has stabilized. Unresolved AEs will be followed until the last scheduled follow-up/EOS visit or until the Investigator and independent MM determine that further follow-up is no longer indicated.

If a participant asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially those related to the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. Wherever possible, the tests and evaluations, including those listed for the EOS/Follow-up visit, should be performed for all participants who discontinue prior to the completion of the study.

# 9. TREATMENT OF PARTICIPANTS

## 9.1. Description of Investigational Product

### 9.1.1. Investigational Product

The IP, CBL-514 is manufactured for subcutaneous injection in compliance with Good Manufacturing Practice regulations. CBL-514 is presented at a concentration of [redacted] at a total volume of 20 mL per vial. The full details of the IP are presented in Table 7.

**Table 7: Investigational Product**

| **Name** | **CBL-514** |
|---|---|
| **Dosage Form** | Solution for injection |
| **Dose Concentration per Vial** | [redacted] |
| **Size of Vial** | 20 mL/vial |
| **Active Ingredient** | [redacted] |
| **Mode of Administration** | Subcutaneous injection |
| **Manufacturer** | [redacted] |
| **Storage** | Store at 4℃<br>Excursions are permitted between 2℃ and 8℃ |

### 9.1.2. Reference Products

Not applicable for this study.

## 9.2. Dosage and Treatment Periods

**Stage 1**: Plan to enroll 12 participants sequentially into 3 dose groups to receive a single course of allocated CBL-514 dose at Visit 2 (Day 1).

**Stage 2:** Plan to enroll up to 20 participants into 1 dose group. Each participant will receive up to 2 courses of CBL-514 at Visit 2 (Day 1) and then at Visit 3 (Visit 2 + 4 weeks [± 7 days]).

## 9.3. Concomitant Medications

All medications, including OTC medications, vitamins, and herbal supplements, taken during the 6 months prior to Screening visit will be recorded in the eCRF and coded using the most current World Health Organization (WHO) drug dictionary available. Prior and concomitant medications will be listed by participant and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (PT). All medications will be reviewed by the Investigator to determine whether the participant is suitable for inclusion in the study.

The use of any IP or investigational medical device within 4 weeks prior to Screening is prohibited. Additional restrictions relating to concomitant medication use are outlined in Section 8.3.1.

Prior therapy or concomitant therapy (after IP administration) with any medications, including both prescription and non-prescription drugs, should be discussed with the Investigator before IP administration, except in the case of necessary treatment of AEs or where appropriate medical care necessitates that therapy should begin before the Investigator can consult with the independent MM.

Paracetamol/acetaminophen (1 to 2 therapeutic doses per week) may be used for minor ailments during the course of the study, at the discretion of the Investigator, without prior consultation with the Sponsor's MM.

## 9.4. Treatment Compliance

All doses will be administered at the investigational site in the presence of the Investigator or their designee.

## 9.5. Protocol Deviations

Should any protocol deviation occur, it must be reported to the study monitor as soon as is reasonably practical. The deviation and the reason for its occurrence must be documented, reported to the relevant IRB (if required), and included in the clinical study report.

## 9.6. Blinding

This is an open label study.

# 10. INVESTIGATIONAL PRODUCT MATERIALS AND MANAGEMENT

## 10.1. Investigational Product

The Sponsor will supply the IP to the investigational site. The IP provided for this study was manufactured under current Good Manufacturing Practices and will be suitable for human use.

## 10.2. Investigational Product Packaging and Labeling

The Sponsor is responsible for the preparation, labeling and providing details of batch numbers, safety, and stability data.

The IP will be labeled in accordance with local regulatory requirements and will be shipped at a temperature of 2℃ to 8℃.

## 10.3. Investigational Product Storage

Upon receipt, the IP must be stored at 4℃. Excursions are permitted between 2℃ and 8℃. Appropriate storage conditions must be ensured either by controlled temperature, or by completing a temperature log in accordance with local requirements on a regular basis (e.g., by temperature logging devices that record every 30 minutes), showing minimum and maximum temperatures reached over the time interval.

The details of storage requirements are outlined in the Pharmacy Manual.

The Investigator or designee will be fully responsible for the security, accessibility, and storage of the IP while it is at the investigational site.

## 10.4. Investigational Product Preparation

CBL-514 is supplied as a ready-to-use solution. Each vial will contain an appropriate volume of CBL-514 with some surplus. Before IP administration to participants, the vials should be warmed up to room temperature. The solution of CBL-514 should be used for subcutaneous injection before the expiry date.

Procedures relating to IP preparation and dispensing are outlined in the Pharmacy Manual.

## 10.5. Administration

The Investigator or designee is responsible for the education of study staff and participants as to the correct administration of the IP.

Details relating to IP administration are outlined in the IP Administration Manual.

## 10.6. Investigational Product Accountability

A record will be maintained by the investigational site that will account for all dispensing and return of any used and unused IP. At the end of the study, the IP will be reconciled, and a copy of the record given to the study monitor.

## 10.7. Investigational Product Handling and Disposal

On completion of the study, any IP remaining at the investigational site will be returned to the Sponsor or its designee in accordance with the Sponsor's instruction. If the destruction of IP is allowed at the investigation site according to the site's internal procedures, any used or unused IP may be destroyed at the investigational site upon receipt of written approval from the Sponsor. Evidence of the destruction of any IP should be supplied to the study monitor and the Sponsor.

# 11. STUDY SCHEDULE

## 11.1. Screening (Day -28 to Day -1)

Prior to enrolling in the study, and before performance of any procedures, participants will attend a screening session during which participants will be screened to assess their eligibility as per the inclusion criteria (Section 8.1) and exclusion criteria (Section 8.2). In addition, during this period participants will be provided with full information concerning details of the study assessments and procedures. They will also be provided with an ICF. Prior to being asked to sign the consent form, participants will be given time to review study information and ask any questions.

After the consent form is signed, screening assessments as delineated in the Schedule of Assessments will be performed (Table 5 and Table 6).

## 11.2. Treatment Visits

Visits and procedures should be completed as delineated in the Schedule of Assessments (Table 5 and Table 6). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

## 11.3. Follow-up Visits

Visits and procedures should be completed as delineated in the Schedule of Assessments (Table 5 and Table 6). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

## 11.4. Early Termination Visit

Visits and procedures should be completed as delineated in the Schedule of Assessments (Table 5 and Table 6). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

**This visit marks the end of participation for participants that withdraw early from the study.**

## 11.5. End of Study (EOS)

Visits and procedures should be completed as delineated in the Schedule of Assessments (Table 5 and Table 6). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

**This visit marks the end of participation in this study.**

# 12. SAFETY ASSESSMENTS

[redacted]

[redacted]

[redacted]

## 12.2. Adverse and Serious Adverse Events

In this study, AEs will be reported for all participants from the time of consent until the completion of the follow-up/EOS visit. Serious adverse events will be reported for all participants (enrolled and not enrolled) from the time of consent. Adverse events reported from the time of consent to Day -1 will be recorded as pre-treatment AEs. Treatment-emergent AEs will be evaluated from the first administration of the IP until the follow-up/EOS visit or the status of AE is recovered/resolved. For AEs that are deemed related to treatment and are ongoing 14 days post EOS/ET for non-serious AEs and 60 days post EOS/ET for SAEs, the outcome will be marked as Recovering/Resolving or Not Recovered/Not resolved on the AE eCRF page.

All spontaneously volunteered and enquired for, as well as observed AEs, will be recorded in the participant's medical records and the eCRF.

### 12.2.1. Definition of Adverse Events

An AE is any event, side-effect, or other untoward medical occurrence that occurs in conjunction with the use of a medicinal product in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IP administration that occur during the reporting periods, even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either the IP or concomitant medications (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if it meets the criteria of an AE.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:

- Time of onset and resolution
- Severity
- Seriousness
- Causality/relation to IP
- Relationship to IP administration procedure
- Action taken regarding IP
- Action taken regarding AE
- Outcome

### 12.2.2. Severity of an Adverse Event

For general AEs, severity of AEs will be graded by the Investigator as one of the following levels:

- **Mild (Grade 1):** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate (Grade 2):** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe (Grade 3):** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- **Life-threatening (Grade 4):** A type of AE that places the participant at immediate risk of death.
- **Death (Grade 5):** Events that result in death.

The NCI-CTCAE v5.0 will be used for more detailed system organ class (SOC).

For expected ISRs, severity will be graded by using the guidance as described in Table 8.

**Table 8: Injection Site Reaction Severity Assessment**

### 12.2.3. Causal Relationship of an Adverse Event

The Investigator will assess the relationship between IP and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to IP will be recorded in the source

documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the IP should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution:

- **Not related:** The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the IP.
- **Unlikely:** The temporal association, participant history, and/or circumstances are such that the IP is not likely to have had an association with the observed event. Other conditions, including concurrent illness, progression, or expression of the disease state, or reaction to a concomitant drug administered appear to explain the event.
- **Possible:** The event follows a reasonable temporal sequence from the time of IP administration or follows a known response to the IP but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Probable:** The event follows a reasonable temporal sequence from the time of IP administration and follows a known response to the IP and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Definite:** The event follows a reasonable temporal sequence from the time of IP administration or control abates upon discontinuation or cannot be explained by known characteristics of the participant's clinical state.

The administration method of CBL-514 is subcutaneous injection. AEs may result from the injection procedure which are not related to the ingredients of the IP. Assessment of causal relationship to IP administration procedure is required and will be recorded in the source documents and the eCRF. The definitions provided in Table 9 are general guidelines to perform the assessment.

**Table 9: Criteria for Determination of Relationship to Drug Administration Procedure**

| | |
|---|---|
| **Drug administration procedure related** | The event is purely caused by or derived from IP injection procedure, including but not limited to anxiety about the injection procedure and vasovagal syncope prior to/during/following injection. |
| **Unable to determine** | The event may be due to both IP and injection procedure. There is no reasonable explanation to determine if IP injection procedure is the only origin to the event. |

Abbreviations: IP = Investigational product.

### 12.2.4. Action Taken with Investigational Products

Should the Investigator need to alter the administration of the IP from the procedure described in the protocol due to the well-being and safety of the participant then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Drug Interrupted
- Drug Withdrawn
- Not Applicable
- Other

### 12.2.5. Outcome

Outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered / Resolved
- Recovering / Resolving
- Recovered / Resolved with Sequelae
- Not Recovered / Not Resolving
- Fatal
- Unknown

## 12.3. Definition of an Adverse Events of Special Interest

The study team should be trained to take particular notice of symptoms/signs suggestive of AESIs in this study.

An AESI is any of the following IP-related events.

1. Skin or fat atrophy that extends > 2 cm from an injection point.
2. Severe injection site pain lasting more than 72 hours.
3. Severe injection site bruising.
4. Any skin hyper or hypopigmentation at the target area and/or the surrounding skin lasting for > 4 weeks.
5. Any skin ulceration at the target area and/or the surrounding skin.
6. Any urticaria at the target area and/or the surrounding skin requiring oral treatment, lasting for > 72 hours.
7. Telangiectasia at the target area and/or the surrounding skin lasting for > 7 days.
8. Local numbness and/or paresthesia lasting for > 7 days.

Occurrence of any of the above AESIs should trigger a review by the Investigator, Sponsor, and MM before the participant who experiences AESI proceeds with the next dose. AESIs are to be reported to the Sponsor within 24 hours upon being noticed by Investigator or designee or being reported by the participant.

## 12.4. Definition of Serious Adverse Event

An SAE is an AE occurring during any study phase (i.e., baseline, treatment, washout, or follow-up), and at any dose of the IP (active or placebo), that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above

Important medical events that may not be one of the above may be considered an SAE by the Investigator when, based upon appropriate medical judgment, they are considered clinically significant and may jeopardize the participant, or may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered 'life-threatening' if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Notes:

* Medical and scientific judgment should be exercised in deciding whether an adverse event/ reaction should be classified as serious in other situations.

* If the participant requires emergency department admission only or undergoes elective surgical treatments these will not be considered an SAE.

### 12.4.1. Notification of a Serious Adverse Event

All SAEs, regardless of relationship to the IP, during the period starting from the time the patient signed the ICF through to the end of study will be recorded in the eCRF. Once the Investigator becomes aware of an SAE, they must report the SAE to the [redacted] within 24 hours of knowledge of the event.

The SAE information will be sent by the investigative site via secure email connection to:

[redacted]

If requested, supporting de-identified source documents (e.g., hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will also be sent to the [redacted].

A written SAE report must include a full description of the event including the below parameters:

- Diagnosis or description of event

- Onset date
- Severity assessment
- Causal relationship to the IP
- Assessment of seriousness of the event
- Corrective treatment administered for the SAE
- Action taken related to IP include the following: dose interruption, dose delay, or IP discontinuation
- Outcome of event and end date

The Sponsor or its representative is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IRB of all SAEs in accordance with the IRB SAE reporting policy. The Investigator will also be notified of all unexpected, serious, drug-related events that occur during the clinical trial. The investigational site is responsible for notifying its IRB of these additional SAEs.

## 12.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events and Serious Adverse Events

Abnormal laboratory findings (e.g., hematology, biochemistry, coagulation, and urinalysis) or other abnormal assessments (e.g., ECG and vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed **clinically significant** by the Investigator and/or delegate or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (and recorded as an SAE if they meet the criteria of being serious) as previously described. Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and SAEs if serious).

The Investigator should exercise medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment is clinically significant. To be considered clinically significant, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

## 12.6. Recording Adverse Events

Adverse events spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded in accordance with the Investigator's normal clinical practice and on the AE page of the eCRF during the study at the investigational site.

However, abnormal values that constitute an SAE or lead to discontinuation of administration of IP must be reported and recorded as an AE. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date

and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study. AEs that occur during the study must be documented in the participant's medical record, on the AE eCRF, and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with baseline values and copies of laboratory reports.

In addition, if the abnormal assessment meets the criteria for being serious, the SAE form must also be completed. A diagnosis, if known, or clinical signs or symptoms if the diagnosis is unknown, rather than the clinically significant laboratory finding or abnormal assessment, should be used to complete the AE/SAE page. If no diagnosis is known and clinical signs or symptoms are not present, then the abnormal finding should be recorded.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.4. An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on a pregnancy form. Pregnancy is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

## 12.7. Follow-up of Adverse Events and Serious Adverse Events

All AEs and SAEs that are deemed related, possibly related, or probably related to the IP must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant dies or is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE/SAE. This may include additional laboratory tests or investigations or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a participant dies during participation in the study or during a recognized follow-up period, the Sponsor should be provided with a copy of any post-mortem findings, including histopathology.

## 12.8. Pregnancy

Pregnancy testing should be performed in all WOCBP throughout the study as per the Schedule of Assessments and the pregnancy results should be captured in the eCRF.

All WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the trial.

If a participant becomes pregnant during the clinical trial, the Investigator will report the details on a pregnancy form to the Sponsor/assigned designee within 24 hours of knowledge of the pregnancy. Even though participants agree to withdraw or terminate the clinical trial, the Investigator should follow-up and document the process and results of all the pregnancies.

Abortions (spontaneous, accidental, or therapeutic) must also be reported to the [redacted] Congenital anomalies/birth defects always meet SAE criteria, and should therefore, be expeditiously reported as an SAE, using the previously described process for SAE reporting. A pregnancy form should also have been previously completed and will need to be updated to reflect the outcome of the pregnancy. The Investigator must report any pregnancy, even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy.

# 13. STATISTICS

Complete details of the statistical analyses and methods, including data conventions, will be provided in the statistical analysis plan (SAP). The SAP will be finalized before the database is locked.

Descriptive statistics will be used to summarize the safety and efficacy data. Dose comparisons will be exploratory in nature.

No adjustments will be made for missing or incomplete data, except for missing efficacy data. Missing efficacy data will be imputed using multiple imputation process (MI SAS procedure) with missing at random (MAR) pattern.

The baseline value is defined as the last available result collected/derived prior to the first investigational drug administration. The change from baseline value is defined as the difference between the result at the post-baseline time point and the baseline value.

Descriptive statistics will consist of the number of observations (n), mean, standard deviation (SD), minimum, median, and maximum for continuous data. Where applicable, 95% confidence intervals (CIs) for the mean may be presented.

Categorical data will be summarized using counts and percentages. Unless specially stated otherwise, the denominator of all percentage calculations will be the number of participants in the treatment group for the specific analysis set.

All collected and derived data will be listed.

## 13.1. Sample Size

No formal sample size calculation has been conducted for this study. The sample size for this study has been chosen based on that considered appropriate for similar types of studies.

Up to 32 participants are planned to be enrolled for this 2-stage study.

## 13.2. Analysis Populations

Participant inclusion into each population will be determined prior to the final analysis.

### 13.2.1. Safety Population

All participants who receive any amount of study treatment will be included in the Safety Population. The Safety Population will be used for summaries and listings of safety and tolerability.

### 13.2.2. Intent-to-Treat Population

The Intent-to-treat (ITT) Population will include all enrolled participants who received at least 1 course of treatment with the IP and have a baseline efficacy assessment and at least 1 post-baseline primary efficacy assessment. The ITT Population will be used for efficacy assessment.

### 13.2.3. Per-Protocol Population

The Per-protocol (PP) Population is a subset of the ITT Population. Participants without any efficacy related major protocol violations, who completed the required dosing schedules of the IP

and 2 follow-up visits after treatment (and completed those visits within the designated visit window), and who had stable body weight during the study (defined as weight change < 3 kg compared to baseline) will be included in the PP Population. The PP Population will be used to repeat efficacy analysis, as relevant.

## 13.3. Statistical Methods

### 13.3.1. Participant Disposition

Participant disposition will be analyzed using counts and percentages. The number and percentage of screened participants, enrolled participants, treated participants, participants in ITT, Safety, and PP populations, participants discontinued from the study and study treatment, as well as the primary reason for discontinuation will be analyzed and listed.

### 13.3.2. Demographics, Medical History, and Baseline Characteristics

Demography and baseline characteristics data will be summarized using descriptive statistics for the Safety Population.

Medical history terms will be coded using the most recent version of MedDRA® available at [redacted]. Medical history will be analyzed using descriptive statistics by MedDRA® SOC and PT for the Safety Population.

### 13.3.3. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the most current version of the WHO drug dictionary available at [redacted]. Prior and concomitant medications will be listed by participant and summarized by treatment using ATC and preferred name for the Safety Population.

### 13.3.4. Treatment Compliance and Exposure

Treatment compliance and exposure will be summarized and listed by treatment for all participants in the Safety Population.

## 13.4. Safety Analyses

All safety assessments, including concomitant medications, AEs, laboratory evaluations, vital signs, ECGs, and other safety assessments will be analyzed using the Safety Population.

### 13.4.1. Adverse Event

Adverse events will be coded using the most current version of the MedDRA® available at [redacted]. A by participant AE data listing, including verbatim term, PT, SOC, severity, and relationship to IP, will be provided. The number of participants experiencing TEAEs and number of individual TEAEs will be summarized by SOC and PT. TEAEs will also be summarized by severity and by relationship to IP.

### 13.4.2. Treatment-Emergent Adverse Events of Special Interest

Adverse events of special interest (as defined in Section 12.3) will be coded using the most current version of the MedDRA® available at [redacted]. A by participant AE data listing, including verbatim term, PT, SOC, severity, and relationship to IP, will be provided. The number of participants experiencing TEAEs and number of individual TEAEs will be summarized by SOC and PT. TEAEs will also be summarized by severity and by relationship to IP.

### 13.4.3. Laboratory Evaluations

Laboratory evaluations (including hematology, biochemistry, coagulation, and urinalysis) will be listed and summarized by treatment and protocol specified collection time point. Observed and change from baseline clinical laboratory data will be summarized each protocol specified collection time point.

The abnormal urinalysis result (dipstick and microscopy), if applicable, will be listed only.

### 13.4.4. Vital Signs

Vital signs (blood pressure [systolic and diastolic], pulse rate, respiratory rate, and tympanic temperature) will be listed and summarized by treatment and protocol specified collection time point. Observed and change from baseline will be summarized at each protocol specified collection time point.

### 13.4.5. Electrocardiograms

ECG values will be listed and summarized by clinical assessment (normal, abnormal but not clinically significant, or abnormal and clinically significant) by treatment by protocol specified collection time point. A summary of change from baseline at each protocol specified time point will also presented. Shift from baseline for ECG clinical assessments will be presented by treatment.

### 13.4.6. Other Safety Assessments

The following assessments will be listed by participant:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

## 13.5. Efficacy Assessments

[redacted]

[redacted]

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

## 14.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented between the Sponsor and the Investigator.

The Sponsor has appointed [redacted] to manage and monitor the study to assure them of the adequate conduct of the study and to act as the contact with the investigational site. A study monitor will be identified and will be responsible for liaison with, and support of, the investigational site.

The study monitor and regulatory authority inspectors are responsible for contacting and visiting the investigative site for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., eCRFs, essential documentation, and other pertinent data) provided that participant confidentiality is respected.

During the study, the monitor will have regular contacts with the investigational site for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs.
- Confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

## 14.2. Data Management

All data will be recorded in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF

information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be subject to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

All eCRFs should be maintained on the system with details of any changes logged accordingly.

## 14.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

## 15.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit.

The study will be carried out in accordance with the current version of the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects), and applicable local regulatory requirements. The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice (GCP) ICH E6 (R2).

## 15.2. Archiving and Regulatory Inspection

All study-related documents and records are to be retained for a minimum of 15 years after trial completion. Written agreement from the Sponsor must precede destruction of the same.

In accordance with ICH GCP, this study may be selected for audit. Inspection of site facilities (e.g., pharmacy, medication storage areas, laboratories) and review of study-related records may occur by the Sponsor, the Sponsor's representative(s), or regulatory authority to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

# 16. ETHICS

## 16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing by an IRB as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any participant into the study.

The Investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB upon receipt of amendments and annually, as local regulations require.

The PI is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the IP (active). The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

## 16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and are consistent with ICH GCP applicable regulatory requirements.

## 16.3. Written Informed Consent

The Investigator will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time without prejudice. The participant should be given the opportunity to ask questions and allowed time to consider the information provided before voluntarily signing the written ICF.

The participant’s signed and dated informed consent must be obtained before conducting any study procedures. The participants will be informed of their rights to privacy but will be made aware that the study data will be submitted to the Sponsor and possibly to drug regulatory authorities for review and evaluation. They will be informed also that the study monitor may inspect their medical records to verify the accuracy and completeness of the study records and results.

The acquisition of informed consent should be documented in the participant’s medical records, as required, and the ICF will be signed and personally dated by the participant and by the person who conducted the informed consent discussion.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the participant or legal representative. The date that informed consent was signed will be recorded on the eCRF.

## 16.4. Data Protection

Participants will be informed that data will be held on file by the Sponsor and that these data may be viewed by staff including the study monitor and by external auditors on behalf of the Sponsor and appropriate regulatory authorities. Participants will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, participants will be identified in such reports only by study identification number, gender, and age. All participant data will be held in strict confidence.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Inspection of Records

The Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, IP stocks, drug accountability records, participant charts and study source documents, and other records relative to study conduct.

## 17.2. Retention of Records

All source data, clinical records and laboratory data relating to the study will be archived for 15 years after the completion of the study. All data will be available for retrospective review or audit.

Source documents are original documents, data, and records from which the participant's eCRF data are obtained. These include, but are not limited to: hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, angiograms, IP accountability logs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to: IRB correspondence, IP accountability logs, and curricula vitae of all personnel participating in the study. These files must be suitable for inspection at any time by the Sponsor, monitor, and/or applicable regulatory authorities. All essential documentation should be retained by the institution for 15 years (or as required by the local regulatory authorities).

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. If the Investigator wishes to assign the study records to another party or move them to another location, the Investigator must notify the Sponsor in writing of the new responsible person and/or the new location.

## 17.3. Liability/Indemnity/Insurance

The Sponsor will ensure sufficient insurance is available to enable it to indemnify and hold the Investigator(s) and relevant staff as well as any hospital, institution, ethics committee or the like, harmless from any claims for damages for unexpected injuries, including death, that may be caused by the IP but only to the extent that the claim is not caused by the fault or negligence of the participants or Investigator(s).

# 18. PUBLICATION POLICY

The publication, presentation, or other public disclosure of study results (each, a 'Publication') will be accurate and honest, undertaken with integrity and transparency and in accordance with the Sponsor's approval.

Publication of results will be subjected to fair peer-review. Authorship will be discussed between researchers prior to study commencement (or as soon as possible thereafter) and reviewed whenever there are changes in participation.

All conflicts arising through disputes about Authorship will be reviewed by the Sponsor. Authorship should be consistent with the guidelines described in the Australian Code for Responsible Conduct of Research (section on Authorship).

Acknowledgment will be given to collaborating institutions and hospitals and other individuals and organizations providing finance or facilities. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

Study data that have not been published, presented, or otherwise disclosed in accordance with the clinical trial agreement shall remain confidential information of the Sponsor. The Investigator may not disclose or permit the disclosure of such unpublished data to any third party, nor may they disclose or permit the disclosure of any study data to any third party in greater detail than the same have been disclosed in any permitted publication, presentation, or other disclosure.

The results summary will be posted to the ClinicalTrials.gov registry as required by legal agreement, local law, or regulation.

# 19. LIST OF REFERENCES

DiBernardo BE. Treatment of cellulite using a 1440-nm pulsed laser with one-year follow-up. Aesthet Surg J. 2011:31(3):328-341.

Hexsel D and Milano PB. Subcision: A treatment for tellulite. Int J Dermatol. 2000:39(7):539-544.

Hexsel D and Dal'Forno T. A validated photonumeric cellulite severity scale. J Eur Acad Dermatol Venereol. 2009:23(5):523-528

Hexsel D, Soirefmann M. Cosmeceuticals for cellulite. Semin Cutan Med Surg. 2011:30(3):167--170.

Nürnberger F and Müller G. So called cellulite: An invented disease. J Dermatol Surg Oncol. 1978:4(3):221-229.

Rossi AM and Katz BE. A modern approach to the treatment of cellulite. Dermatol Clin. 2014: 32(1):51-59.

# 20. APPENDICES

## 20.1. Appendix 1: Reference images of treatment area

[redacted]

## 20.2. Appendix 2: Reference List of Prohibited Substances (CYP inhibitors and inducers only)

[redacted]

| | | |
|---|---|---|
| [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] |

## 20.3. Appendix 3: Contraceptive Methods

[redacted]