CLINICAL STUDY PROTOCOL

STUDY TITLE:	**A 2-Stage Adaptive Design, Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of CBL-514 Injection for Reducing Abdominal and Thigh Subcutaneous Fat**
PROTOCOL NUMBER:	CBL-0202
DEVELOPMENT PHASE:	2
STUDY DRUG:	CBL-514
INDICATION:	Reducing subcutaneous fat in adults.
SPONSOR:	Caliway Biopharmaceuticals Australia Pty Ltd 58 Gipps Street, Collingwood 3066 Vic, Australia
AUTHORS:	[redacted]

VERSION HISTORY

Protocol	Date	Type of Amendment
Protocol Version 1.3	11 Nov 2020	New protocol
Protocol Version 2.0	18 Jan 2021	Amendment to Stage 2 of study design
Protocol Version 3.1	04 May 2021	Amendment to treatment area (This version was submitted to Australia ethics committee only.)
Protocol Version 3.2	28 May 2021	Substantial amendments to treatment area, study drug injection, and efficacy endpoint. (This version was submitted to US FDA only.)
Protocol Version 4.0	13Aug 2021	Amendment to Stage 2 of study (This version was submitted to US FDA only.)
Protocol Version 4.1	09 Sep 2021	Amendment to Stage 2 of study (This version was submitted to US Institutional Review Board only.)
Protocol Version 5.0	13 Oct 2021	Amendment to Stage 2 of study (This version was submitted to US Institutional Review Board only.)
Protocol Version 5.1	20 Oct 2021	Substantial amendment (This version was submitted to Australia ethics committee only.)
Protocol Version 5.2	12 Jan 2022	Minor revisions to include further details in relation to position of the Reference point recording and IP administered surrounding the Reference point. Reference to Image Procedure manual also added.
Protocol Version 6.0	18 Jul 2022	Substantial amendment
Protocol Version 7.0	23 Nov 2022	Amendment to study endpoints
Protocol Version 7.1	17 Jan 2023	Amendment to study endpoints
Protocol Version 8.0	01 Mar 2023	Amendment to study endpoints

PROTOCOL AUTHORIZATION

Title: A 2-Stage Adaptive Design, Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of CBL-514 Injection for Reducing Abdominal and Thigh Subcutaneous Fat

As Caliway Biopharmaceuticals Australia Pty 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 Conference on Harmonisation guidelines on Good Clinical Practice (GCP).

Signature Date

[redacted] / Director

Name / Title

Caliway Biopharmaceuticals Australia Pty Ltd

INVESTIGATOR'S AGREEMENT

Title: A 2-Stage Adaptive Design, Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of CBL 514 Injection for Reducing Abdominal and Thigh Subcutaneous Fat

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 Review Board (IRB)/Independent Ethics Committee (IEC). 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 subjects.

I have read the protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with GCP guidelines, the Declaration of Helsinki, and local regulations (as applicable).

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.

Investigator: _____

Printed name

Investigational Site:

Signed: _____ Date: _____

Signature of Investigator

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Study Project Manager	[redacted]	Caliway Biopharmaceuticals Australia Pty Ltd [redacted]
Medical Monitor / 24-hour Emergency Contact	[redacted]	[redacted]

2. SYNOPSIS

Name of Sponsor/Company:
Caliway Biopharmaceuticals Australia Pty Ltd.

Name of Investigational Product:
CBL-514

Name of Active Ingredient:
[redacted]

Protocol Number:
CBL-0202

Title of Study:
A 2-Stage Adaptive Design, Phase 2 Study to Evaluate the Efficacy, Safety and Tolerability of CBL-514 Injection for Reducing Abdominal and Thigh Subcutaneous Fat

Study Center(s):
Multicenter

Phase of Development:
Phase 2

Objectives:

Primary Objectives:

Stage 1:

- Evaluate the safety and tolerability of injection lipolysis with CBL-514.

Stage 2:

- Assess the proportion of subjects who lose at least 150 mL of subcutaneous fat volume as measured by ultrasound compared with placebo

Secondary Objectives:

Stage 1:

- Assess the efficacy of single course of CBL-514 at applicable dose levels in reducing subcutaneous fat over the treated area as measured by ultrasound compared with Baseline.

Note: no efficacy endpoints/objectives will be assessed for Group 1 of Stage 1 study.

Stage 2:

- Assess the proportion of subjects who lose at least 200 mL of subcutaneous fat volume as measured by ultrasound compared with placebo
- Evaluate the number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
- Assess the efficacy of up to 4 courses of CBL-514 in reducing subcutaneous fat volume over the treated area as measured by ultrasound compared with placebo
- Assess the efficacy of up to 4 courses of CBL-514 in reducing subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline
- Evaluate safety following up to 4 courses of CBL-514 when compared with placebo.

Methodology:

This is a 2-stage adaptive design, Phase 2 study to evaluate the efficacy, safety, and tolerability of CBL-514 injection for reducing subcutaneous fat. This Phase 2 study has an integrated design consisting of a single ascending dose (SAD) part in Stage 1 followed by a parallel-arm, placebo-controlled design in Stage 2. A total of approximately 99 adult subjects (n = 24 [Stage 1]; n = 75 [Stage 2]) with

- thigh subcutaneous fat thickness of at least 1.00 cm (10.0 mm) and up to 4.00 cm (40.0 mm) measured by ultrasound at Screening and Day 1, for Group 1 in Stage 1,
- abdominal subcutaneous fat thickness of at least 2.00 cm (20.0 mm) and up to 5.0 cm (50.0 mm) measured by ultrasound at Screening and Day 1 for Group 2-4 in Stage 1,
- and abdominal skinfold thickness of at least 3.00 cm (30.0 mm) and up to 8.00 cm (80.0 mm) by pinch method (measured by calibrated caliper) at Screening for Stage 2,

will be enrolled across the 2 stages of the study.

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

The Stage 1 will include a total of 24 subjects enrolled in 4 sequential escalating CBL-514 dose groups: 320 mg, 480 mg, 640 mg and 800 mg. The groups will be open label. The 4 groups will each include 6 subjects.

Subjects in Group 1 (320 mg) will receive CBL-514 injections on thighs, with total allocated dose of IP evenly divided into 2 thighs. Subjects from Group 2 to 4 (480 mg-800 mg) will receive CBL-514 injections on abdomen with allocated dose of IP.

Based upon Safety Review Committee (SRC) recommendation intermediate doses may be explored.

Local effects of CBL-514 injection will be evaluated, and blood samples will be taken and analyzed to assess the safety of CBL-514. The dosing scheme is presented in the Table S1 below:

Table S1: Dosing Scheme - Stage 1

Group	Treatment area	CBL-514 Dose Level (mg/cm^2)	Injection volume per injection in 4 cm^2 grid space	Administration for one dose			
				No. of Injection	Total Injection Volume of CBL-514* (mL)	Total CBL-514 (mg)	
1	Thighs	2.0	1.6 mL	40 / 20 (total/ per thigh)	64 / 32 (total/ per thigh)	320	[redacted]
2	Abdomen	2.0	1.6 mL	60	96	480	[redacted]
3	Abdomen	2.0	1.6 mL	80	128	640	[redacted]
4	Abdomen	2.0	1.6 mL	100	160	800	[redacted]

							[redacted]

*The concentration of CBL-514 is 5 mg/mL.

Subjects will be screened for inclusion and exclusion criteria during a 28-day screening period (Day -28 to Day -1). At the Treatment visit (Day 1), eligible subjects will be sequentially assigned to receive one course of allocated CBL-514 dose.

Subjects will visit the site on each of the study visits. Subjects will remain onsite for observation for at least 1 hour after the administration of the IP, or longer at the discretion of the Investigator, and until all planned assessments for the visit are completed.

An Early Termination (ET) visit has been planned for subjects who are withdrawn from the study earlier than planned for assessment as soon as possible after early withdrawal, no later than 6 weeks from the last dose received.

A subject diary will be provided to each subject, to record if there are any changes to the injection site/s or any discomforts from Day 1 until last clinic visit or when all injection site reactions (ISRs) have resolved or stabilized. Subjects will be instructed to bring the subject diary with them for all visits to the clinic.

During Stage 1 of the study, the SRC will meet after all subjects in a dose group complete the Week 1 visit. The SRC will review all reported adverse events (AEs), adverse event of special interests (AESIs), laboratory trends, and vital signs of all subjects 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 progressing to the next dose group.

The safety and tolerability data of CBL-514 from Stage 1 will be reviewed by the SRC before commencement of Stage 2. A top-level summary of safety data will be submitted to the relevant Institutional Review Board /Independent Ethics Committee (IRB/IEC) for review before proceeding to Stage 2 of the study.

Stage 2 (multiple-dose, randomized, single-blind, parallel-group, placebo-controlled study)

Stage 2 of the study will be initiated after IRB/EC review of a top-level summary of safety data from Stage 1 of the study. Stage 2 will be conducted as a single-blind, placebo-controlled study and will assess a single dose level of CBL-514. The dose of CBL-514 used in the Stage 2 will be set no higher than the highest safe dose from Stage 1. Each subject will receive up to 4 treatments of allocated CBL-514 (2 mg/cm²) or placebo administered on abdomen, once every 4 weeks. The minimum dose is 300 mg per treatment and the maximum dose is 600 mg per treatment. The dose adjustment will depend on the level of fat accumulation on subject's abdomen at the discretion of the Investigator.

[redacted] The minimum dose of 300 mg with 25 injections must be administered. It is at the discretion of the Investigator to perform dose adjustment for any dose over the minimum dose administration, which will depend on the level of fat accumulation on subject's abdomen. The maximum dosing scheme is presented in Table S2 below.

Table S2: Maximum Dosing Scheme - Stage 2

Group	CBL-514 Dose Level (mg/cm^2)	Injection volume per injection in 6.0 cm^2 grid space	Administration for one dose			
			No. of Injection	Total Injection Volume of IP (mL)	Total CBL-514 (mg)	
CBL-514	2.0	2.4 mL	50	120	600	[redacted]
Placebo	-	2.4 mL	50	120	-	-

In Stage 2 of the study, considering drop-out rates (16% CBL-514 group vs 44% placebo group), approximately 75 subjects are planned to be enrolled and randomized 2:1 (50 subjects in the CBL-514 group and 25 subjects in the placebo group) in order to have a total of 56 evaluable subjects. Randomization scheme is shown in Table S3: Randomization Scheme – Stage 2, below.

Table S3: Randomization Scheme - Stage 2

Planned Enrolled Subjects: 75 (2:1)		Planned Evaluable Subjects 56 (3:1)	
CBL-514 Group - pre-drop out	Placebo Group - pre drop out	CBL-514 Group - post drop-out	Placebo Group - post drop-out
50	25	42	14

Subjects should have sufficient subcutaneous fat on the abdomen to receive injections on Day 1. This will be based on eligibility criteria as set out in inclusion criterion 3. Before administration, the Investigator should evaluate whether a subject is able to receive the minimum dose, 300 mg (25 injections) as defined by Study Drug Administration Manual. [redacted] If a subject is not able to receive the minimum dose, the ongoing treatment and post-dose assessments will be cancelled, and the remaining treatment visits would not be required for that subject. For subjects that do not complete 4 treatments due to not enough residual fat, the subject will be requested to continue with follow-up visits (Visits 6 and 7). This arrangement would not be regarded as missing protocol required visits, or as discontinuation from the study.

According to the schedule of assessments, the first follow up visit (Visit 6) should be performed 4 weeks post the final treatment. If treatment is cancelled at Visits 3, 4 or 5 due to the insufficient abdominal fat, it is recommended that the first follow up visit is performed on the same day of the treatment cancellation. If not, then +7 days visit window should be utilized to schedule another day to complete the first follow up visit.

If a subject cannot complete the 4 treatments and withdraws from the study for reasons other than dose adjustment, only the ET visit should be performed for final follow-up.

Subjects will be screened for inclusion and exclusion criteria during a 28-day screening period (Day -28 to Day -1). At Visit 2 (Day 1), eligible subjects will be randomized (2:1) to receive either CBL-514 or placebo. As Stage 2 of the study is a randomized, single-blind, parallel-group, placebo-controlled study, Subjects will be blinded to IP allocation in Stage 2.

Subjects will visit the site on each of the study visits and will remain onsite for observation for 1 hour after the administration of IP, or shorter/ longer at the discretion of the Investigator and until all planned assessments for the visit are completed.

An ET visit has been planned for subjects who are withdrawn from the study earlier than planned for assessment as soon as possible after early withdrawal, no later than 6 weeks from the last dose received.

A subject diary will be provided to each subject to record if there are any changes to the injection site/s or any discomforts in between visits. Subjects will be instructed to bring the subject diary with them for all visits to the clinic.

SRC meeting

Safety oversight will be provided by an SRC comprising the Investigator, the Sponsor's Representative and Medical Monitor (MM). The SRC will be established prior to Screening. The details of SRC will be set out in an SRC Charter.

During Stage 1 of the study, the SRC will meet after all subjects in a dose group complete the Week 1 visit. The SRC will review all reported AEs, AESIs, laboratory trends, and vital signs of all subjects 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 progressing to the next dose group.

Before commencement of Stage 2, the SRC will review and evaluate safety data. A top-level summary of safety data will be submitted to the relevant IRB/IEC for review before proceeding to Stage 2 of the study. Planned dosing for Stage 2 will be based on a review of the safety data from Stage 1.

In addition, occurrence of any of AESI or any AE that, based on the judgment of Investigator, raises a medical concern, should trigger a review by the SRC before proceeding with the dose escalation/s in Stage 1 or before proceeding with the next course of treatment in Stage 2.

For SRC meetings, safety assessments will include the following:

- Incidence of all AEs
- AESI
- Changes from Baseline in clinical laboratory test results
- Changes from Baseline in vital signs.

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

Definition of Adverse Event of Special Interest

An AESI is any event which may be of medical concern specific to the IP.

Occurrence of any of the below mentioned AESI should trigger a review by the SRC before proceeding with the dose escalation/s (Stage 1) or the next dose (Stage 2):

1. Fat atrophy that extends > 2 cm from an injection point or is > 10% of the treated area or is associated with tenderness lasting > 24 hours.
2. Pain limiting self-care activities of daily living (ADL) lasting more than 72 hours after active intervention (e.g. analgesic).
3. Skin atrophy that extends beyond area of any erythema or induration or is > 10% of the treated area or is associated with tenderness lasting > 24 hours.
4. Any skin hyper or hypopigmentation at the target area and/or the surrounding skin lasting for > 4 weeks.

   * The color change reflecting from the bruising color is not included. The color changes due to deposition or loss of pigment in epidermal tissue is considered as hyper or hypopigmentation.
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.

Above mentioned AESIs are to be reported to the Sponsor within 24 hours upon notification by Investigator and/or delegates.

Study Stopping Criteria:

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

- Any subject experiences an adverse event as Grade 3 (as defined in the National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0) for cardiovascular, renal or hepatic event considered to be at least possible related to IP,
- Except for cardiovascular, renal, or hepatic events specified in Criterion #1, any participant experiences an AE as Grade 4 and considered to be at least possibly related to IP;
- Any subject experiences a serious adverse event (SAE) that is considered to be at least possibly related to IP;
- 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 of these criteria occur, consultation between the Sponsor representative, the Investigator, and the MM will take place as soon as possible to evaluate the event. Subjects should remain in the study and be followed until the adverse event resolves or stabilizes.

Prohibitions and Restrictions in the Study

Medication

During the entire duration of the study (from Screening visit to end of study [EOS]/ET visit) use of following medications, treatment modalities, or diets are prohibited:

a. Use of drugs for weight loss e.g. Orlistat (Xenical), Naltrexone HCl/Bupropion HCl (Contrave), etc.,
b. Use of anticoagulant/antiplatelet therapy or medications or dietary supplements which impede coagulation or platelet aggregation,
c. Any cosmetic or interventional surgery procedures on area to be treated,
d. Use of terfenadine (Teldane), buspirone (Buspar), fexofenadine (Fexotabs, Tefodine, Telfast, Xergic, Allegra, etc.), any medication that is known to strongly inhibit or induce CYP enzymes (please refer to Section 24.1), sensitive CYP substrates or drugs with narrow therapeutic index, in the opinion of the investigator, may affect the evaluation of the study product or place the participant at undue risk.
   If a subject requires the use of above mentioned therapeutic agents during the study for any reason, these therapeutic agents should not be used at least for 2 days prior to dosing and until 1 day post-dose.
e. Use of other investigational drug or device within 4 weeks prior to Screening.
f. Use of medication which is delivered via subcutaneous injection at the treatment area during the study period

Subjects should be advised not to take any prescription and over-the-counter (OTC) medications without consulting the Investigator.

Contraception

Highly effective contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly should be used. The list below is based on the recommendation of the Clinical Trial Facilitation Group (CTFG 2014).

- 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[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomized partner [1,2]
- sexual abstinence[3]
- condom used by male partner during sexual intercourse.

Contraceptive requirements for male subjects with Women of childbearing potential (WOCBP) partner: A male subject should use condom during heterosexual intercourse and avoid sperm donation from the time of the first dose of study drug, throughout study participation until 12 weeks after the last study drug dose. For the WOCBP partner, contraception recommendations should also be considered.

[1] Contraception methods that in the context of this guidance are considered to have low user dependency.

[2] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception. This is applicable for both female and male subjects.

Number of Subjects (Planned):

Approximately 99 adult male or female subjects will be enrolled for the 2-stage study.

A total of 24 subjects are planned to be enrolled in 4 sequential groups in Stage 1 of the study. Approximately 75 subjects are planned to be enrolled in Stage 2 of the study. Subjects in Stage 2 will be randomized 2:1 (i.e., CBL-514 group: 50 subjects; placebo group: 25 subjects) in order to have 56 evaluable subjects for the 2 groups. The sample size for stage 2 of the study was calculated based on currently accepted standards for exploratory investigation design.

Inclusion Criteria:

To be eligible for this study, a subject must meet ***all*** of the following inclusion criteria:

1. Male or female, aged 18 years to 64 years old (at Screening), inclusive.
2. Body mass index (BMI) > 18.5 and < 35 kg/m^2 and body weight ≥ 50 kg at Screening and Day 1.
3. Subject has sufficient subcutaneous fat thickness surrounding the center of localized area of treatment.
   a. For Group 1 (320 mg) in Stage 1, thigh subcutaneous fat thickness of at least 1.00 cm (10.0 mm) and up to 4.00 cm (40.0 mm) measured by ultrasound at Screening and Day 1.
   b. For Group 2-4 (480 mg-800 mg) in Stage 1, abdominal subcutaneous fat thickness of at least 2.00 cm (20.0 mm) and up to 5.00 cm (50.0 mm) measured by ultrasound at Screening and Day 1.
   c. For Stage 2, abdominal skinfold thickness of at least 3.00 cm (30.0 mm) and up to 8.00 cm (80.0 mm) by pinch method (measured by calibrated caliper) at Screening.
4. Subject has stable body weight (identified as ≦ 5% weight change per subject report) for at least 3 months before Screening and during the study.
5. Subject who has maintained a stable lifestyle (e.g. exercise, eating patterns, and smoking habit) per subject report for at least 3 months before Screening and during the study.
6. Voluntarily signs the Informed Consent Form (ICF) 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.

Exclusion Criteria:

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

1. Female subject 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. Male subject who is not willing to commit to an acceptable contraceptive method.

   Note: Subjects who are not of childbearing potential are not required to use contraception. Females with no childbearing potential are defined as who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are post-menopausal (defined as at least 50 years with ≥ 12 months of amenorrhea with a follicle stimulating hormone (FSH) > 40 IU/L).
2. Subject diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation.
3. Subject has hemoglobin A1c (HbA1c) ≥ 9%, delayed wound healing, or any diabetic risks which, in the opinion of Investigator, is inappropriate to participate in the study.
4. Subject has a clinically significant cardiovascular disease and abnormal findings in electrocardiogram (ECG).
5. Subject with active or prior history of malignancies within 5 years before Screening or being worked-up for a possible malignancy. Except adequately treated basal cell carcinoma of skin and in situ squamous cell carcinoma of skin would be eligible as per Investigator's discretion.
6. Subject with a history of human immunodeficiency virus (HIV)-1, infection or subjects with active HIV infection at Screening with positive HIV antigen/antibody (Ag/Ab) combo test.

7. Subject with a history of Trypanophobia, the extreme fear of medical procedures involving injections or needles, or who experience vasovagal syncope and faint or pass out at the sight of blood or a needle.
8. Subject has abnormal skin or local skin conditions at the treatment area, which in the opinion of Investigator, is inappropriate to participate in the study, including but not limited to any of the following:
   a. Skin manifestations of a systemic disease,
   b. Any abnormality of the skin or soft tissues of the area to be treated,
   c. Grade III cellulite (Nürnberger and Muller scale, Nürnberger F, 1978) at the area to be treated,
   d. Skin folding or fat folding on abdomen
   e. Sensory loss or dysesthesia in the area to be treated,
   f. Evidence of any cause of enlargement in the area to be treated other than localized abdominal or thigh subcutaneous fat,
   g. Tattoos on the area to be treated.
9. Subject who has undergone the following procedures:
   a. Previous surgery which caused scar tissues on the anticipated treatment area before Screening or during the study, except laparoscopic surgery and surgery which cause very small scar tissues would be eligible as per Investigator's discretion,
   b. Liposuction to the region to be treated before Screening or during the study,
   c. Esthetic procedure e.g. cryolipolysis, ultrasonic lipolysis, low level laser therapy (LLLT), lipolysis injection to the region to be treated within 12 months before Screening or during the study.
   d. Using medication which is delivered via subcutaneous injection at the treatment area during the study period.
10. Subject is on prescription or OTC weight reduction medication or weight reduction programs within 3 months before Screening or during the study.
11. Subject is undergoing chronic steroid or immunosuppressive therapy, with the exception of oral steroid inhalation indicated for asthma management or topical steroid application for skin conditions that are not directly applied or indirectly affect the treatment area.
12. Requiring continual use of the following therapeutic agents during the study: terfenadine (Teldane), buspirone (Buspar), fexofenadine (Fexotabs, Tefodine, Telfast, Xergic, Allegra, etc.), any medication that is known to strongly inhibit or induce CYP enzymes (please refer to Section 24.1), sensitive CYP substrates or drugs with narrow therapeutic index, in the opinion of the investigator, may affect the evaluation of the study product or place the participant at undue risk.
    If a subject 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 prior to dosing and until 1 day post-dose.
13. Unable to receive local anesthesia (e.g., history of hypersensitivity to lidocaine).
14. Subjects with known allergies or sensitivities to the IP or its components.
15. Subjects with liver cirrhosis, 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), or with any hepatic medical condition that would interfere with assessment of safety or efficacy or compromise the subject's ability to undergo study procedures or provide informed consent.

16. Subjects 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. Subjects who are currently on dialysis should be excluded.
    Subjects 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 subjects may be eligible upon the Investigator's assessment.
17. Use of other investigational drug or device within 12 weeks prior to Screening.

Withdrawal criteria

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

Stage 1

1. Subject withdraws consent.
2. Between Screening and Day 1, subjects whose overall body weight change of ≥ 3kg.
3. Subject has body weight change ≥ 5 % based on Day 1 body weight.
4. Any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the subject.
5. Subject who cannot complete follow-up visits within 6 weeks post treatment visit.

Stage 2

1. Subject withdraws consent.
2. Subject has body weight change ≥ 3 kg compared to Day 1 body weight during the whole study period.
3. Subject has body weight change ≥ 3 kg during the follow-up period compared to the body weight from the last treatment visit.
4. Any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the subject.
5. Subjects has a treatment interval > 6 weeks in length between any of the dosing courses.
6. Subject cannot complete at least the first follow-up visit (Visit 6 / end of treatment [EOT]) within 6 weeks post final treatment visit, or cannot complete the second follow-up visit (Visit 7 / EOS) within 10 weeks post final treatment visit.
7. Subject has efficacy related major protocol violation at Day 1 (baseline)

Investigational Product, Dosage and Mode of Administration:

Table S4: CBL-514 Product Details

Name	**CBL-514**
Dosage Form	Solution for Injection

Dose Concentration Per Vial	5 mg/mL
Size of Vial	20 mL/vial
Active Ingredient	[redacted]
Mode of Administration	Subcutaneous injection
Storage	Store at 4°C (39°F), excursions are permitted between 2°C and 8°C

Duration of Treatment:

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

Stage 1

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

Stage 2

Each subject will participate in Stage 2 of the study for approximately 20 weeks, including a Baseline visit on Visit 2 (Day 1), 1 visit every 4 weeks during the treatment period (Visits 3, 4, and 5), and 2 follow-up visits at Visit 6 (Visit 5+ 4 weeks) and 7 (Visit 5+ 8 weeks).

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

Reference Therapy, Dosage and Mode of Administration:

Placebo

The placebo to be used in the study will be commercially available (isotonic) Sodium Chloride for injection (0.9% NaCl). Equivalent volume of Sodium Chloride injection will be administered by subcutaneous injection.

Criteria for Evaluation:

Primary Endpoints

Stage 1

The primary endpoints of Stage 1 of the study are:

- Safety and tolerability following single dose of CBL-514 as assessed by recording of treatment emergent adverse events (TEAEs), laboratory assessments, vital signs, ECGs, physical examinations, and injection site assessment.

Stage 2

The primary endpoints of Stage 2 of the study are:

- The proportion of subjects who lose at least 150 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.

  [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]

Secondary Endpoints

Stage 1

The secondary endpoints of Stage 1 of the study are:

- Reduction of subcutaneous fat thickness as measured by ultrasound compared with Baseline. [Time frame: Day 1 and Week 4]
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound

compared with Baseline.
[Time frame: Day 1 and Week 4]

*Note: no efficacy endpoints/objectives will be assessed for Group 1 of Stage 1 study.

Stage 2

The secondary endpoints of Stage 2 of the study are:

- The proportion of subjects who lose at least 200 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.
  [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]
- Number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
  [Time frame: from Visit 2 (Baseline) to Visit 7]
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound from Baseline to follow-up visits compared with placebo.
  [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]
- Reduction of subcutaneous fat volume over the treated area of the CBL-514 group as measured by ultrasound compared with individual Baseline.
  [Time frame: Visit 2 (Baseline), Visit 3, Visit 4, Visit 5, Visit 6 and Visit 7]
- Safety as assessed by recording of TEAEs, laboratory assessments, vital signs, ECGs, physical examinations, and ISRs compared with placebo.

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. No formal hypothesis testing is planned, and dose comparisons will be exploratory in nature.

No adjustments will be made for missing or incomplete data, except for missing efficacy data which may be imputed using multiple imputation.

The Baseline value is defined as the last available result collected/derived prior to the first treatment 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 specifically stated otherwise, the denominator for all percentage calculations will be the number of subjects in the treatment group for the specific analysis set. Where applicable, 95% CIs (Clopper-Pearson) may be presented.

All collected and derived data will be listed.

Analysis Populations

Intent-to-treat population:

The intent-to-treat (ITT) population will include all enrolled or randomized subjects who received at least one course of IP treatment

Safety Population:

All subjects who receive at least one confirmed dose of IP will be included in the safety population. Subjects will be analyzed according to the treatment they actually receive. The safety population will be used for summaries and listings of safety, tolerability, and drug exposure data.

Per protocol population:
Stage 1

- A subset of ITT
- Subjects without any efficacy related major protocol violations
- Subjects who complete the proposed dosing schedule of study drug and complete all follow-up visits after treatment
- Subjects whose body weight remain stable throughout the study, identified as having body weight change < 3% based on Day 1 body weight

However, a subject who was discontinued due to an AE, or died before the required exposure could be met, will still be included in this population.

Stage 2

- A subset of ITT
- Subjects without any efficacy related major protocol violations
- Subjects who complete all proposed dosing schedules of study drug and complete 2 follow-up visits after treatment (including the subject who has dose adjustment judged by the Investigator)
- Subjects have all visits of IP administration within 6 weeks.
- Subjects whose body weight remain stable throughout the study, identified as having body weight change < 2.5 kg compared to last visit and change of body weight < 3 kg compared to Day 1 body weight.
- Subjects whose Visit 6 is performed 3 to 5 weeks post final treatment
- Subjects whose Visit 7 is performed 7 to 9 weeks post final treatment

However, a subject who was discontinued due to an AE, or died before the required exposure could be met, will still be included in this population.

Safety and Tolerability Assessment

Safety and Tolerability assessment is the primary objective of Stage 1 of the study and secondary objective of Stage 2 of the study.

All safety assessments, including AEs, laboratory evaluations, vital signs, ECGs, physical examination, ISR 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 subject 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 subjects 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.

Safety data from Stage 1 will be reviewed during the SRC meeting before commencement of Stage 2 of the study. A top-level summary of safety data will be submitted to the relevant IEC/IRB for review

before proceeding to Stage 2 of the study.

Efficacy Assessments

Efficacy will be analyzed in both Stage 1 and Stage 2 of the study.

Stage 1

Efficacy endpoints to be analyzed in Stage 1 are:

- Reduction of subcutaneous fat thickness as measured by ultrasound compared with Baseline
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline.

*Note: no efficacy assessments will be done for Group 1 of Stage 1 study.

The reduction of subcutaneous fat thickness and subcutaneous fat volume over the treated area will be summarized with descriptive statistics. An estimate of the 95% CI for the mean reduction in subcutaneous fat thickness and corresponding p-value will also be provided.

The analysis set for the primary efficacy analysis is the ITT population. The primary analysis will be repeated using the PP population, as relevant. Exploratory analyses may be performed to assess differences between the dose levels.

Full details of all efficacy analyses will be provided in the SAP.

Stage 2

Primary efficacy endpoints to be analyzed in Stage 2 are:

- The proportion of subjects who lose at least 150 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.

Secondary efficacy endpoints to be analyzed in Stage 2 are:

- The proportion of subjects who lose at least 200 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.
- Number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with placebo
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline

For the primary endpoint, the proportion of subjects who lose at least 150 mL of subcutaneous fat will be summarized for CBL-514 and placebo, respectively, along with their 95% confidence intervals.

The analysis set for the primary efficacy endpoint is the ITT population. The primary analysis will be repeated using the PP population, as relevant. Exploratory analyses may be performed to assess differences between treatments.

All analyses will be performed without adjustment for multiple endpoints.

Full details of all efficacy analyses will be provided in the SAP.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
Ag/Ab	Antigen/antibody
ALT	Alanine aminotransferase
ALKP/ALP	Alkaline phosphatase
ASAPS	American Society for Aesthetic Plastic Surgery
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
β-hCG	Beta human chorionic gonadotropin
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
ET	Early termination
FDA	Food and Drug Administration
FBS	Fasting blood sugar
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
HED	Human equivalent dose
HIFU	High intensity focused ultrasound
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection site reaction
ITT	Intent-to-treat
IUD	Intrauterine device
LDL	Low-density lipoprotein
LLLT	Low level laser therapy
MedDRA®	Medical Dictionary for Regulatory Activities
MM	Medical monitor
NOAEL	No-observed-adverse-effect-level
OTC	Over-the-counter
PP	Per protocol
PT	Preferred term
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SRC	Safety Review Committee
TBIL	Total bilirubin

Abbreviation or Specialist Term	Explanation
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
US	United States
VAS	Visual Analogue Scale
WBC	White blood cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

5. FACILITIES AND PERSONNEL

Table 3: Facilities and Personnel

Sponsor	Caliway Biopharmaceuticals Australia Pty Ltd [redacted]
Local Australian Sponsor	Caliway Biopharmaceuticals Australia Pty Ltd [redacted]
Local MM	[redacted]

6. BACKGROUND AND INTRODUCTION

6.1. Introduction

6.1.1. Unmet Medical Need

The focus on body aesthetics and appearance continues to influence the treatment-seeking behavior of several people in the modern society. The most popular body contouring approaches used to improve the cosmesis of subcutaneous fat deposits are surgical and include liposuction, abdominoplasty, and thigh lifts, among other procedures. This increasing demand has led to the rapid growth and development of noninvasive, non-surgical treatment techniques. Although surgical techniques can result in the most pronounced outcomes in respect to improved body contouring results, they are also associated with inherent risk and complications such as pain, swelling, prolonged recovery, scarring, hematoma or infection, which make noninvasive procedures increasingly popular (Adatto MA, 2014; Kennedy J, 2015).

The risks, financial costs and lengthy downtime associated with surgical procedures for fat reduction have led to the development of a number of noninvasive techniques (Kennedy J, 2015). In the recent years, noninvasive body contouring techniques have become one of the most widespread procedures and are growing fast in areas of esthetic medicine (Nestor MS, 2013). Noninvasive treatment approaches are painless, safe, and require little to no downtime (Adatto MA, 2014).

According to reported data by the American Society for Aesthetic Plastic Surgery (ASAPS) in 2013, the significant risk of invasive body contouring procedures has led to 521% growth of noninvasive techniques since 1997 (Rotunda AM, 2006). In addition, it has been estimated that noninvasive body contouring procedures are growing by 21% annually (Atiyeh BS, 2008). Even for shortening postoperative recovery, decreasing bruising and more skin tightening, surgical lipectomy techniques are combined with noninvasive methods (Atiyeh BS, 2008).

Commonly used treatment options for abdominal and thigh subcutaneous fat have been limited to invasive surgical or non-surgical procedures. Lipoplasty (including thigh liposuction) was the second most popular procedure performed by ASAPS members in 2019, with 270,670 procedures performed. Thigh lifts were performed at a rate of 9,815 in 2019 by ASAPS members (ASAPS, 2019). Unfortunately, surgical liposuction under general anesthesia carries significant potential risk and complications to a person seeking an aesthetic improvement; 2 independent surveys of board-certified aesthetic plastic surgeons in the United States (US) determined the mortality rate to be approximately 20 deaths per 100,000 procedures (Grazer FM, 2000). As for non-surgical procedures, there are now numerous options for fat reduction which utilize medical devices to deliver certain frequency of energy or cold temperature through the skin to ablate subcutaneous fat cells in the anterior abdomen, such as radiofrequency (RF), high intensity focused ultrasound (HIFU), Cryolipolysis or LLLT (Friedmann DP, 2015). In many cases (e.g., cryolipolysis, HIFU), these non-surgical procedures also cause inflammation which is related to the mechanism of removing the ablated fat cells from the treated area (Jalian HR, 2012). This inflammatory process may result in pain, swelling and redness along with the increased recovery time for the process to complete and time to view aesthetic benefit. In addition, the cost of these devices as well as the disposables required must be taken into consideration for each treatment.

There is another non-surgical treatment for reducing subcutaneous fat which is known as mesotherapy or lipodissolve, a minimally invasive procedure. Mesotherapy involves a series of injections of medications that are purported to melt away localized fat deposits. Combinations of drugs such as phosphatidylcholine and deoxycholate (commonly called PC and DC, respectively), DC alone or combinations including other drugs or products such as vitamins, minerals, and herbal extracts may be used (Rotunda AM, 2006, Atiyeh BS, 2008). However, warning letters were issued by the Food and Drug Administration (FDA) to medical spas offering mesotherapy for unfounded claims of efficacy (Atiyeh BS, 2008, Duncan D, 2011). There were also numerous reports of significant AEs (e.g., skin necrosis, infections, etc.) due to unregulated mesotherapy (Atiyeh BS, 2008, Duncan D, 2011). This creates an unmet medical need to develop an injectable alternative with promising efficacy and an acceptable safety profile to fulfill the need of reducing abdominal and thigh subcutaneous fat.

6.1.2. Overview of CBL-514

CBL-514 Injection (CBL-514), is a new injection for lipolysis product developed by Caliway Biopharmaceuticals Co., Ltd. The product is supplied with 20 mL in a glass vial with a stopper. Each mL of CBL-514 contains 5 mg the drug substance, the CBL-514 Powder, with [redacted] serving as the active pharmaceutical ingredients. CBL-514 is compatible to use with needle and syringe for subcutaneous injection.

CBL-514 has shown promising efficacy and safety profiles in prior research in *in vitro* and animal models for the proposed indication in promoting adipose cell apoptosis.

6.2. Summary of Nonclinical and Clinical Studies

6.2.1. Nonclinical Studies

CBL-514 has undergone an extensive nonclinical safety and efficacy evaluation. These nonclinical studies conducted for CBL-514 are described in detail in the CBL-514 IB.

The mechanism of action of CBL-514 is to trigger adipocyte apoptosis by inhibition of DYRK1b, thereby increasing the expression of Caspase-3 and Bax/Bcl-2 ratio, which are apoptosis biomarkers. Our pervious nonclinical study results demonstrated that CBL-514 induced cell death of adipocyte through apoptosis mechanism and reduced the subcutaneous fat in treatment area.

[redacted]

[redacted]

6.2.2. Clinical Studies

The safety and tolerability of injection lipolysis with CBL-514, PK profile of and preliminary efficacy of 4 doses of CBL-514 in reducing abdominal subcutaneous fat at the target area was evaluated in a first-in-human, placebo-controlled, double-blind, Phase 1/2a study (CBL-16001) in Australia. In the Phase 1 component of CBL-16001, CBL-514 was administered in human for the assessment of safety and tolerability. The treatment was a SAD design in which 9 proposed dosing cohorts were involved (Cohorts 1 to 9). In 9 sequential cohorts, CBL-514 dose levels were 2 mg, 10 mg, 20 mg, 40 mg, 40 mg, 80 mg, 160 mg, 240 mg, and 320 mg per subject. For Cohorts 1 to 5, both CBL-514 and placebo groups were administered on each side of abdomen in a blinded manner to evaluate the possible AEs attributed to the components of CBL-514. For Cohorts 6 to 9, only CBL-514 was dosed in subjects.

Overall, Phase 1 results in physical examination, vital signs, ECG, and laboratory tests, including biochemistry, hematology, coagulation, and urinalysis, all showed favorable profiles for the safety of CBL-514. While there was no systemic TEAE from CBL-514, the most frequent TEAEs were ISRs.

[redacted]

[redacted]

In the Phase 1 component of CBL-16001, CBL-514 was well tolerated through the ascending dose escalation scheme from 2 mg to 320 mg.

6.3. Rationale for the Study

To date, the nonclinical and clinical study data suggest that subcutaneous administration of CBL-514 may be effective in reducing subcutaneous fat 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).

6.4. Dosage and Treatment Periods

The study is divided into 2 stages:

Stage 1

Stage 1 will include a total of 24 subjects enrolled in 4 sequential escalating CBL-514 dose groups and will receive a single course of CBL-514: 320 mg, 480 mg, 640 mg, and 800 mg. The groups will be open label. The 4 groups will each include 6 subjects.

Subjects in Group 1 (320 mg) will receive CBL-514 injections on thighs, with total allocated dose of IP evenly divided into 2 thighs. Subjects from Group 2 to 4 (480 mg-800 mg) will receive CBL-514 injections on abdomen with allocated dose of IP. The dosing scheme is presented in Table 7.

Stage 2

In Stage 2 of the study, a total of 75 subjects will be randomized to 2:1 (i.e., 50 subjects in the CBL-514 group and 25 subjects in the placebo group). Each subject will receive up to 4 courses of CBL-514 or placebo. Each course of CBL-514/placebo will be administered 4 weeks apart, over a period of up to 12 weeks. Only a single dose level of CBL-514 will be administered in Stage 2, which will be set no higher than the highest safe dose from Stage 1 of the study.

6.4.1. Rationale for Dose Selection

The maximum dose of this Phase 2 study is estimated based on the 8-week repeated-dose GLP toxicity studies in Sprague-Dawley rats and Beagle dogs, respectively.

[redacted]

[redacted]

[redacted]

Furthermore, the completed Phase 1/2a Study (protocol number: CBL-16001) had evaluated the safety of CBL-514 injection for reducing abdominal subcutaneous fat. Single treatment of CBL-514 were administered with dose levels of 2 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 240 mg, and 320 mg per subject, which have shown overall favorable results in physical examination, vital signs, ECG, laboratory tests including biochemistry, hematology, coagulation, and urinalysis profiles.

There was no systemic TEAEs from CBL-514, the most frequent TEAEs were ISRs. During SAD progress, the severity and duration of common ISRs did not show apparent difference among cohorts, which provided even more evidence on the safety of CBL-514 in human.

Based on the nonclinical and clinical results above, the dose escalation groups in the present study are structured as 320 mg, 480 mg, 640 mg, and 800 mg to assess safety and tolerability of higher doses of CBL-514 when injected in abdominal or thigh adipose tissue.

The doses used in this study are 2 mg/cm^2, which are all within the pharmacologically active dose range. (Please refer to IB for more details) Moreover, the Phase 1 component of CBL-16001 study have assessed safety in human from 0.5 ~ 2 mg/cm^2 with favourable safety profiles. Based on the results of the CBL-16001 Phase 1 study, the incidence of TEAEs reported were similar across all dose cohorts especially in Cohort 5 to 9, where subjects received the same unit dose (2 mg/cm^2) over an increasing treatment area/ total dose per Cohort. Therefore, CBL-0202 has adopted the similar design to have a consistent unit dose, 2 mg/cm^2, throughout the study. It is expected that the severity or incidence of adverse events in CBL-0202 study will not increase compared to the completed study, even though the dose used is higher.

The purpose of increasing the total dose in CBL-0202 study is to accommodate the larger treatment area needed to cater different needs of subjects due to various shape of abdomen/ thighs and level of fat accumulation, so as to reach meaningful efficacy and to also improve on the overall appearance and shape to achieve aesthetically pleasing result for the subjects.

6.5. Subject Population

The study will be conducted in male and female subjects aged 18 to 64 years (inclusive at the time of informed consent) with

- thigh subcutaneous fat thickness of at least 1.00 cm (10.0 mm) and up to 4.00 cm (40.0 mm) measured by ultrasound at Screening and Day 1 for Group 1 in Stage 1,
- abdominal subcutaneous fat thickness of at least 2.00 cm (20.0 mm) and up to 5.00 cm (50.0 mm) measured by ultrasound at Screening and Day 1 for Group 2-4 in Stage 1,
- and abdominal skinfold thickness of at least 3.00 cm (30.0 mm) and up to 8.00 cm (80.0 mm) by pinch method (measured by calibrated caliper) at Screening for Stage 2.

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 IP (see Section 9). WOCBP must demonstrate negative pregnancy testing at Screening and before administration of 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).

6.6. 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). The conduct of the study will be in accordance with the International Conference for Harmonisation (ICH) Integrated Addendum to E6(R1): Guideline for ICH GCP E6(R2), annotated with comments by the Australian Therapeutic Goods Administration (TGA; 2018).

This study will be conducted under a protocol reviewed and approved by an IRB/IEC and investigations will be undertaken by scientifically and medically qualified persons; where the benefits of the study are in proportion to the risks.

7. TRIAL OBJECTIVES AND PURPOSE

7.1. Objectives

7.1.1. Primary Objectives

7.1.1.1. Stage 1

The primary objective of Stage 1 of the study is to:

- Evaluate the safety and tolerability of injection lipolysis with CBL-514

7.1.1.2. Stage 2

The primary objectives of Stage 2 of the study are to:

- Assess the proportion of subjects who lose at least 150 mL of subcutaneous fat volume as measured by ultrasound compared with placebo

7.1.2. Secondary Objectives

7.1.2.1. Stage 1

The secondary objectives of Stage 1 of the study are to:

- Assess the efficacy of single course of CBL-514 at applicable dose levels in reducing subcutaneous fat over the treated area as measured by ultrasound compared with Baseline.

*Note: no efficacy endpoints/objectives will be assessed for Group 1 of Stage 1 study.

7.1.2.2. Stage 2

The secondary objectives of Stage 2 of the study are to:

- Assess the proportion of subjects who lose at least 200 mL of subcutaneous fat volume as measured by ultrasound compared with placebo
- Evaluate the number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
- Assess the efficacy of up to 4 courses of CBL-514 in reducing subcutaneous fat volume over the treated area as measured by ultrasound compared with placebo
- Assess the efficacy of up to 4 courses of CBL-514 in reducing subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline
- Evaluate safety following up to 4 courses of CBL-514 when compared with placebo

7.2. Endpoints

7.2.1. Primary Endpoints

7.2.1.1. Stage 1

The primary endpoints of Stage 1 of the study are:

- Safety and tolerability following single dose of CBL-514 as assessed by recording of TEAEs, laboratory assessments, vital signs, ECGs, physical examinations, and injection site assessment.

7.2.1.2. Stage 2

The primary endpoints of Stage 2 of the study are:

- The proportion of subjects who lose at least 150 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.
  [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]

7.2.2. Secondary Endpoints

7.2.2.1. Stage 1

The secondary endpoints of Stage 1 of the study are:

- Reduction of subcutaneous fat thickness as measured by ultrasound compared with Baseline. [Time frame: Day 1 and Week 4]
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline. [Time frame: Day 1 and Week 4]

*Note: no efficacy endpoints/objectives will be assessed for Group 1 of Stage 1 study.

7.2.2.2. Stage 2

The secondary endpoints of Stage 2 of the study are:

- The proportion of subjects who lose at least 200 mL of subcutaneous fat as measured by ultrasound from Baseline to follow-up visits compared with placebo.

  [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]

- Number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
  [Time frame: from Visit 2 (Baseline) to Visit 7]

- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound from Baseline to follow-up visits compared with placebo. [Time frame: Visit 2 (Baseline), Visit 6 and Visit 7]

- Reduction of subcutaneous fat volume over the treated area of the CBL-514 group as measured by ultrasound compared with individual Baseline. [Time frame: Visit 2 (Baseline), Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7]

- Safety as assessed by recording of TEAEs, laboratory assessments, vital signs, ECGs, physical examinations, and ISRs compared with placebo

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a 2-stage adaptive design, Phase 2 study to evaluate the efficacy, safety, and tolerability of CBL-514 injection for reducing abdominal or thigh subcutaneous fat. This Phase 2 study has an integrated design consisting of a SAD part in Stage 1. Stage 2 will be conducted as a single-blind, placebo-controlled study, with 1 treatment group and 1 placebo group. A total of approximately 99 adult subjects with

- thigh subcutaneous fat thickness of at least 1.00 cm (10.0 mm) and up to 4.00 cm (40.0 mm) measured by ultrasound at Screening and Day 1, for Group 1 in Stage 1,
- abdominal subcutaneous fat thickness of at least 2.00 cm (20.0 mm) and up to 5.00 cm (50.0 mm) measured by ultrasound at Screening and Day 1 for Group 2-4 in Stage 1,
- and abdominal skinfold thickness of at least 3.00 cm (30.0 mm) and up to 8.00 cm (80.0 mm) by pinch method (measured by calibrated caliper) at Screening for Stage 2,

will be enrolled across the 2 stages of the study.

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

Stage 1 will include a total of 24 subjects enrolled in 4 sequential escalating CBL-514 dose groups and will receive a single course of CBL-514: 320 mg, 480 mg, 640 mg, and 800 mg. The groups will be open label. The 4 groups will each include 6 subjects.

Subjects in Group 1 (320 mg) will receive CBL-514 injections on thighs, with total allocated dose of IP evenly divided into 2 thighs. Subjects from Group 2 to 4 (480 mg-800 mg) will receive CBL-514 injections on abdomen with allocated dose of IP.

Based upon SRC recommendation intermediate doses may be explored.

The dosing scheme is presented in Table 7.

A schematic of the study design is provided in Figure 1. Local effects of CBL-514 injection will be evaluated, and blood samples will be taken and analyzed to assess the safety of IP.

Subjects will be screened for inclusion and exclusion criteria during a 28-day screening period (Day -28 to Day -1). At the Treatment visit (Day 1), eligible subjects will be sequentially assigned to receive 1 course of allocated CBL-514 dose.

Subjects will visit the site on each of the study visits. Subjects will remain onsite for observation for at least 1 hour after the administration of CBL-514, or longer at the discretion of the Investigator and until all planned assessments for the visit are completed.

Subjects who are withdrawn from the study earlier than planned should attend an ET visit as soon as possible after early withdrawal, no later than 6 weeks from the last dose received.

A subject diary will be provided to each subject, to record if there are any changes to the injection site/s or any discomforts from Day 1 until last clinic visit or when all ISRs have resolved or stabilized. Subjects will be instructed to bring the subject diary with them for all visits to the clinic.

During Stage 1 of the study, the SRC will meet after all subjects in a dose group have completed the Week 1 visit. The SRC will review all reported AEs, AESIs, laboratory trends, and vital signs of all subjects 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 progressing to the next dose group.

The safety and tolerability data of CBL-514 from Stage 1 will be reviewed by the SRC before commencement of Stage 2 (see Section 8.3). A top-level summary of safety data will be submitted to the relevant IRB/IEC for review before proceeding to Stage 2 of the study.

Study visits and assessments for Stage 1 of the study will occur as delineated in the Schedule of Assessments (Table 4).

Stage 2 (multiple-dose, randomized, single-blind, parallel, placebo-controlled study)

Stage 2 will be conducted as a single-blind study, with 1 CBL-514 group and 1 placebo group. Each subject will receive up to 4 treatments of allocated CBL-514 (2 mg/cm²) or placebo administered on abdomen, once every 4 weeks. The minimum dose is 300 mg per treatment and the maximum dose is 600 mg per treatment. The dose adjustment will depend on the level of fat accumulation on subject's abdomen at the discretion of the Investigator.

Stage 2 of the study will be initiated after IRB/EC review of top-level summary of safety data from Stage 1 of the study. The dose for Stage 2 will be based on a review of the safety data from Stage 1 of the study and the dose for Stage 2 will be set no higher than the highest safe dose from Stage 1.

In Stage 2, subjects will be randomized 2:1 CBL-514 group vs placebo group. Considering drop-out rates, approximately 75 subjects will be enrolled (50 subjects in the CBL-514 group and 25 subjects in the placebo group) in order to have 56 evaluable subjects for the 2 groups.

Subjects should have sufficient subcutaneous fat on their abdomen to receive injections on Day 1. This will be based on eligibility criteria set out in inclusion criterion 3. Before administration, the Investigator should evaluate whether a subject is able to receive the minimum dose, 300 mg (25 injections) as defined by Study Drug Administration Manual. [redacted] If a subject is not able to receive the minimum injection dose, the ongoing treatment and post-dose assessments will be cancelled and the remaining treatment visits would not be required for that subject. For subjects that do not complete 4 treatments due to not enough residual fat, the subject will be requested to continue with follow-up visits (Visit 6 and 7). This arrangement would not be regarded as missing protocol required visits, or as discontinuation from the study.

If a subject cannot complete the 4 treatments and withdraws from the study because of reasons except for dose adjustment, only the ET visit should be performed for final follow-up.

Subjects will be screened for inclusion and exclusion criteria during a 28-day screening period (Day -28 to Day -1). At Visit 2 (Day 1), eligible subjects will be randomized 2:1: (i.e., CBL-514 group: 50 subjects; placebo group: 25 subjects) to receive CBL-514 or placebo, respectively.

Subjects will visit the site on each of the study visits and will remain onsite for observation for 1 hour after the administration of the IP, or shorter/ longer at the discretion of the Investigator and until all planned assessments for the visit are completed.

An ET visit has been planned for subjects who are withdrawn from the study earlier than planned for assessment as soon as possible after early withdrawal, no later than 6 weeks from the last dose received.

A subject diary will be provided to each subject to record if there are any changes to the injection site/s or any discomforts in between visits. Subjects will be instructed to bring the subject diary with them for all visits to the clinic.

Study visits and assessments for Stage 2 of the study will occur as delineated in the Schedule of Assessments presented in Table 5.

8.2. Number of Subjects

Approximately 99 adult male or female subjects, will participate in the study. A total of 24 subjects are planned to be enrolled in 4 sequential groups in Stage 1 of the study. Considering drop-out rates, approximately 75 subjects are planned to be enrolled and randomized 2:1 (i.e., 50 subjects in the CBL-514 group and 25 subjects in the placebo group) in order to have 56 evaluable subjects in Stage 2 of the study. The sample size for stage 2 of the study was calculated based on currently accepted standards for exploratory investigation design.

8.3. Dose Adjustment and Safety Oversight

Study drug administration should be in accordance with dose scheme. The deviation of administration will potentially affect the study drug efficacy. The following major deviations will be deemed to have an influence on efficacy. Effort should be made to adhere to study design.

1. Subject who is assigned to wrong dose group
2. Subject with dosing compliance* less than 90% or more than 110% of total dosage per treatment (except for the subject who has dose adjustment judged by the Investigator[#]).

*Compliance is defined as the taken dosage out of the total dose in the assigned dose group or number of injections out of the amount required per treatment in accordance with protocol.
[#]During Stage 2, before administration, the Investigator should evaluate whether a subject is able to receive the minimum dose, 300 mg (25 injections) as defined by Study Drug Administration Manual. [redacted] If a subject is not able to receive the minimum dose, the ongoing treatment and post-dose assessments will be cancelled, and the remaining treatment visits would not be required for that subject. For subjects that do not complete 4 treatments due to not enough residual fat, the subject will be requested to continue with follow-up visits (Visit 6 and 7). This arrangement would not be regarded as missing protocol required visits, or as discontinuation from the study.

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

During Stage 1 of the study, the SRC will meet after all subjects in a dose group complete the Week 1 visit. The SRC will review all reported AEs, AESIs, laboratory trends, and vital signs of all subjects 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 progressing to the next dose group.

Before commencement of Stage 2, the SRC will review safety data. A top-level summary of safety data will be submitted to the relevant IRB/IEC for review before proceeding to Stage 2 of the study.

In addition, the occurrence of any of AESI or any AE that, based on the judgment of Investigator, raises medical concern, will trigger a review by the SRC before proceeding with dose escalation/s in Stage 1 or course of treatment in Stage 2.

For the SRC meeting, safety assessments will include the following:

- Incidence of all AEs
- AESI
- Changes from Baseline in clinical laboratory test results
- Changes from Baseline in vital signs.

If at any time the study is terminated, a written statement fully documenting the reasons for termination will be provided to the relevant IRB/IEC (see Section 8.5).

8.4. Stopping Criteria

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

- Any subject experiences an adverse event as Grade 3 (as defined in the NCI-CTCAE version 5.0) for cardiovascular, renal or hepatic event considered to be at least possibly related to IP,
- Except for cardiovascular, renal, or hepatic events specified in Criterion #1, any participant experiences an AE as Grade 4 and considered to be at least possibly related to IP
- Any subject experiences an SAE that is considered to be at least possibly related to the IP
- 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 PP may not be safe.

If any of these criteria occur, consultation between the Sponsor representative, the Investigator, and the MM will take place as soon as possible to evaluate the event. Subjects should remain in the study and be followed until the adverse event resolves or stabilizes.

8.5. Criteria for Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety or efficacy of the IP indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for subjects participating in the study. This may

be determined by the Sponsor, the Investigator, the IRB/IEC, or regulatory authorities.

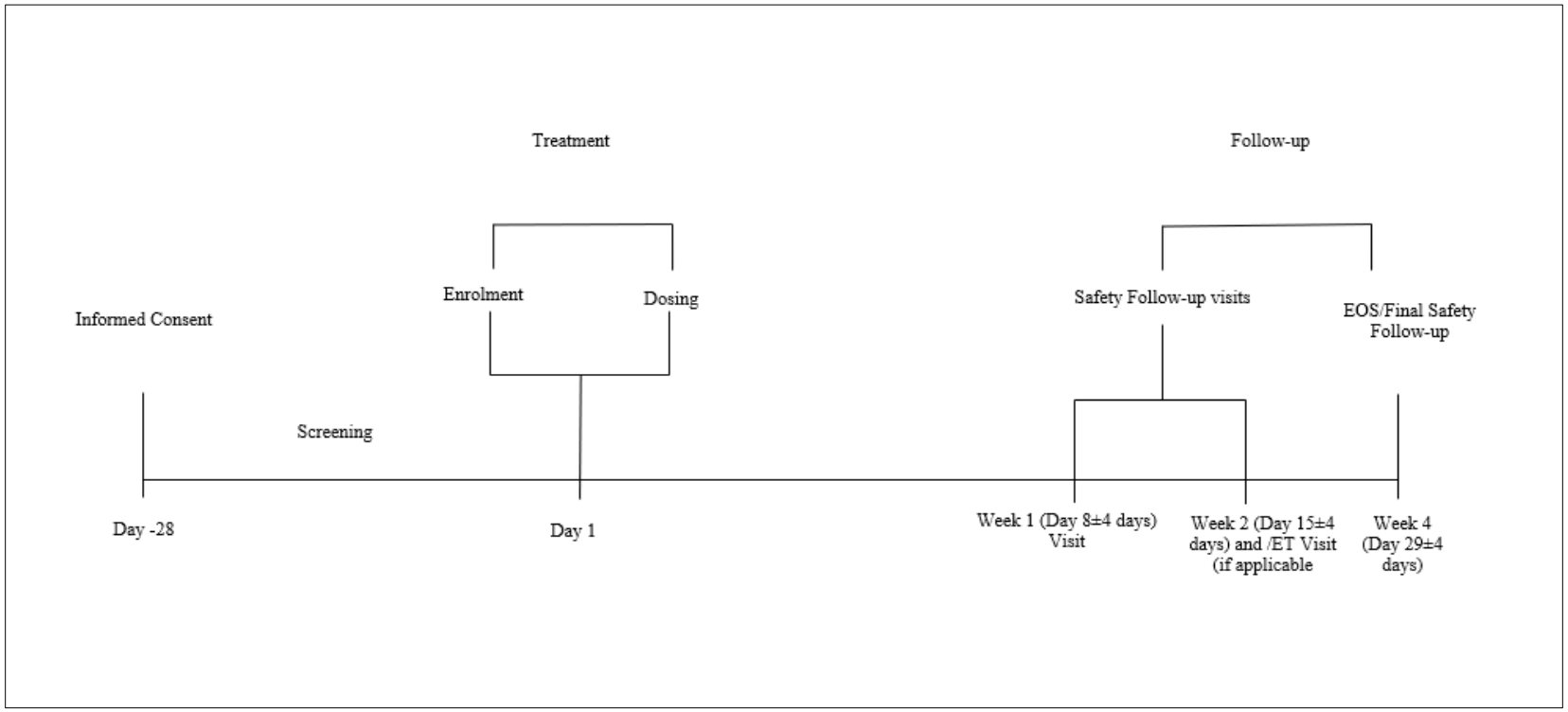
- The study is terminated by the Sponsor for administrative reasons.

The Sponsor, Investigator, the IRB/IEC and the regulatory authority reserve the right to terminate or suspend the study at any time; however, termination or suspension of the study 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 eCRFs. If the Sponsor, the IRB/IEC, or regulatory authority elects to terminate or suspend the study or the participation of the investigational site, a study-specific procedure for ET 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 the IRB/IEC and/or regulatory authority in writing of the study's completion or early discontinuation.

Figure 1: Study Design

Stage 1



Stage 2

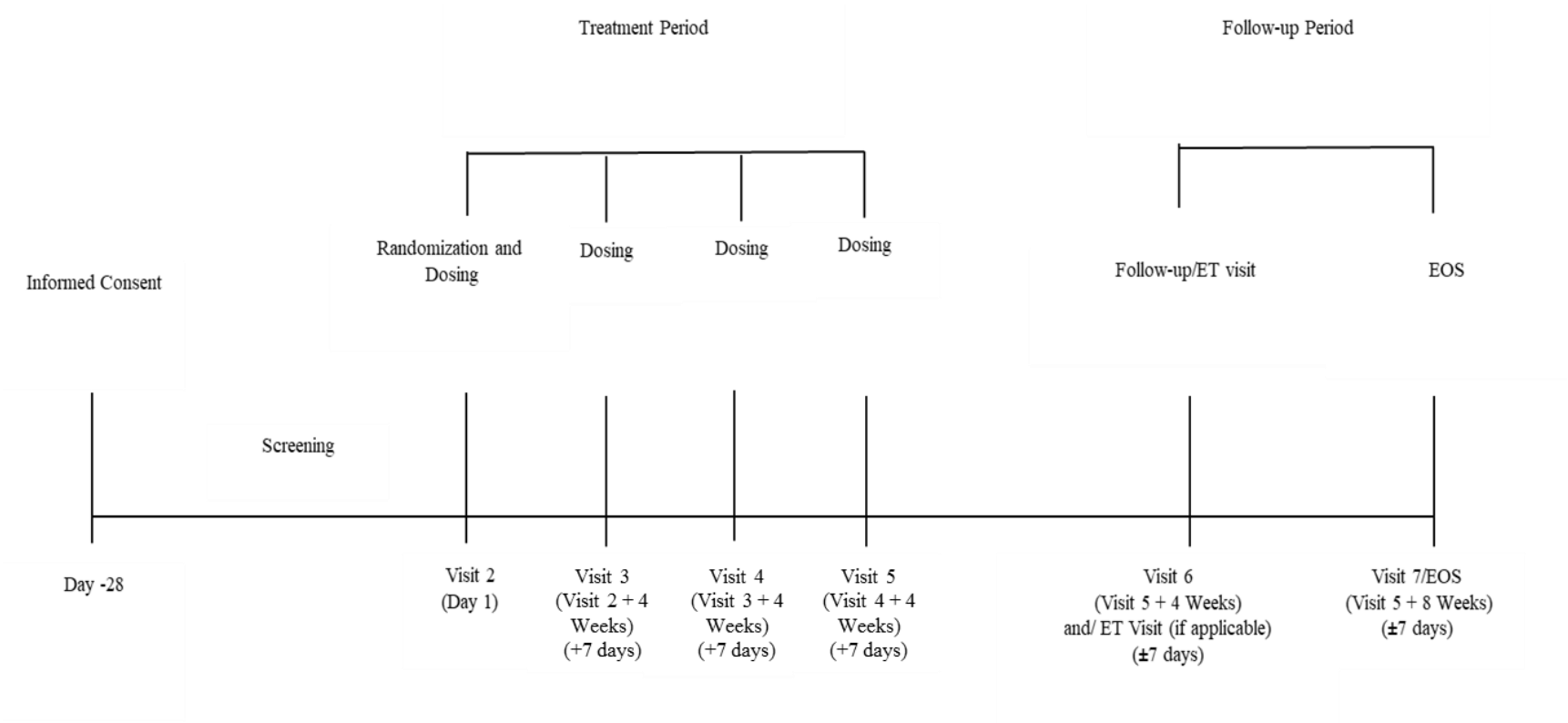

Treatment Period
Follow-up Period
Randomization and Dosing
Dosing
Dosing
Dosing
Informed Consent
Follow-up/ET visit
EOS
Screening
Day -28
Visit 2 (Day 1)
Visit 3 (Visit 2 + 4 Weeks) (+7 days)
Visit 4 (Visit 3 + 4 Weeks) (+7 days)
Visit 5 (Visit 4 + 4 Weeks) (+7 days)
Visit 6 (Visit 5 + 4 Weeks) and/ ET Visit (if applicable) (±7 days)
Visit 7/EOS (Visit 5 + 8 Weeks) (±7 days)

Table 4: Schedule of Assessments - Stage 1

Assessment	**Screening**	**Treatment**	**Follow-up**		
Stage 1	**Screening**	**Day 1***	**Week 1**	**Week 2**	**Week 4**
Day	**-28 to -1**	**1**	**8 ± 4 days**	**15 ± 4 days**	**29 ± 4 days**
Visit	**1**	**2**	**3**	**4/ ET**	**5 /EOS**
Informed Consent	X				
Inclusion/Exclusion	X	X			
Demographics	X				
Medical History and Prior Medications[1]	X				
Subject Diary[2]		X	X	X	X
Anthropometric Parameter[3]	X	X	X[18]	X	X
Abdominal or Thigh Ultrasound[4]	X	X		X[17]	X
Medical Examinations					
Physical Examination[5]	X	X	X[16]	X[16]	
Injection site assessments[6]		X	X	X	X
Vital Signs[7]	X	X	X[16]	X[16]	
ECG[8]	X	X	X[16]	X[16]	
Laboratory Evaluation					
Blood Tests[9]	X	X	X[16]	X[16]	
Urinalysis[10]	X	X	X[16]	X[16]	
Pregnancy Status[11]	X	X		X[16]	
Virology[12]	X				

Assessment	Screening	Treatment	Follow-up		
Stage 1	**Screening**	**Day 1***	**Week 1**	**Week 2**	**Week 4**
Day	**-28 to -1**	**1**	**8 ± 4 days**	**15 ± 4 days**	**29 ± 4 days**
Visit	**1**	**2**	**3**	**4/ ET**	**5 /EOS**
IP Administration		X			
Photography[13]		X	X	X	X
AE[14]		X	X	X	X
Concomitant Medication		X	X	X	X[15]

AE: Adverse event; AESI: Adverse event of special interest; Ag/Ab: Antigen/antibody; ALP/ALKP: Alkaline phosphatase; ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; AST: aspartate aminotransferase; β-hCG: Beta human chorionic gonadotropin; ECG: Electrocardiogram; eGFR: Estimated glomerular filtration rate; EOT: End of treatment: EOS: End of study; ET: Early Termination; FBS: Fasting blood sugar; GGT: Gamma-glutamyl transferase; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; HBV: Hepatitis B Virus; Hct: Hematocrit; HCV: Hepatitis C Virus; HDL-C: High-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; INR: International normalized ratio; IP: Investigational product; ISR: Injection site reaction; LDL-C: Low-density lipoprotein cholesterol; RBC: Red blood cell; SAE: Serious adverse event; TBIL: Total bilirubin; WBC: White blood cell; WOCBP: Woman of childbearing potential.

* Available measurements of clinical evaluations (physical examinations, vital signs, and ECG) and laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis) within 14 days prior to IP dose can be accepted as the Baseline value and will not necessitate duplicate examinations.

* If study drug dose is within 7 days of Screening pregnancy test, pregnancy test at Visit 2 (Day 1) will not be necessary to assess.

* In cases where more than 1 data is available for a certain evaluation, the latest value prior to the study drug administration will be used as the Baseline value.

[1] Details of concurrent medical conditions, prior surgical procedures, and chronic diseases or other significant medical events prior to Screening will be collected. Any other non-significant medical events within 6 months prior to Screening will also be collected. Prior medications include a complete history of previous treatment/medications within 6 months prior to Screening.

[2] Subject diaries will be provided to the subjects on Day 1. The subjects will be asked to record if there are any changes to the injection site/s or any discomforts from Day 1 until last clinic visit or when all ISRs have resolved or stabilized. The diary will be reviewed at the following visits as needed.

[3] Anthropometric parameters to be collected include body height and body weight. Body height will be measured at Screening

only. Thigh circumference will be collected only for Group 1 (320 mg) in Stage 1 study.

[4] Ultrasound – Thickness of fat will be obtained by ultrasonic measurements across target area. Abdominal or thigh ultrasound will be performed at Screening, Day 1, and Week 4. Abdominal or thigh ultrasound may be performed within 4 days before Day 1 and up to 4 days before/after Week 4 follow-up visit. Day 1 ultrasound can be exempted if the screening ultrasound is performed within 4 days prior to IP dose, and the screening ultrasound can be accepted as the Baseline value.

[5] A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

[6] On Day 1, injection site assessments will be performed pre-dose and at 1-hour post-dose.

[7] On Day 1, vital signs assessments to be performed pre-dose and at 1-hour post-dose. Vital sign assessments include temperature, pulse rate, blood pressure, and respiratory rate. At simultaneously scheduled assessments, vital signs will be collected prior to any blood draws.

[8] On Day 1, ECG assessments will be performed pre-dose only. ECG to be performed in supine position after at least 5 minutes rest. The following ECG parameters will be recorded: heart rate, RR interval, PR interval, QT interval, QTc interval, and QRS interval.

[9] Blood tests include biochemistry, hematology, and coagulation assessments. Biochemistry assessments include albumin, ALT, AST, ALP, triglyceride, total cholesterol, LDL-C, HDL-C, TBIL, GGT, urea, creatinine, eGFR, HbA1c, FBS, Sodium, Potassium, Bicarbonate, and Chloride. Hematological assessments include Hb, Hct, RBC count, mean corpuscular volume, Leukocyte/white blood cell (WBC) count, WBC differential, and platelet count. Coagulation assessments include aPTT, Prothrombin time, and INR.

[10] Urinary samples for dipstick will be collected. On Day 1, collection will be performed pre-dose only.

[11] Serum β-hCG test will be taken for WOCBP at Screening visit only. FSH test is required for females who are post-menopausal at the Screening visit. Urine β-hCG strip test will be taken WOCBP for other scheduled visits.

[12] Virology tests include HIV/HBV/HCV infection test. Active HIV infection is detected by detectable positive HIV Ag/Ab combo test; active HBV: HBsAg; active HCV: positive anti-HCV antibody.

[13] On Day 1, photography will be performed pre-dose and at 1 hour post-dose on Day 1. Other timepoints on Day 1 can be added to record the ISR at the discretion of the Investigator.

[14] The occurring AEs/SAEs (including AESI) will be followed until resolution or the event is considered stable.

[15] Collected only if a medication is related to AEs following the visit 4.

[16] Assessment/collection can be performed on or within 4-days window prior to visit date.

[17] Abdominal or thigh ultrasound only applicable to ET visit and not required for Week 2 visit.

[18] At Week 1, only body weight will be measured and collected for anthropometric parameter.

Table 5: Schedule of Assessments – Stage 2

Assessment/Schedule	Screening	Treatment				Follow-up	
Visit	**1**	**2**	**3**	**4**	**5/EOT**	****6/ET**	**7/EOS**
Day	**-28 to -1**	**1***	**(Visit 2 + 4 weeks)**	**(Visit 3 + 4 weeks)**	**(Visit 4 + 4 weeks)**	**(Visit 5 + 4 weeks)**	**(Visit 5 + 8 weeks)**
Visit window		-	**+ 7days**	**+ 7days**	**+ 7days**	**± 7days**	**± 7days**
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics	X						
Medical History and Prior Medications[1]	X						
Subject Diary		X	X	X	X	X[14]	X[14]
Anthropometric Parameter[2]	X	X	X	X	X	X	X
Efficacy Assessment							
Abdominal Ultrasound[3]		X	X	X	X	X	X
9-Point CBL-514 Satisfaction Questionnaire						X	
Medical Examinations							
Physical Examination[4]	X	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]
Injection site assessments[5]		X	X	X	X	X	X
Vital Signs[6]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
ECG[7]	X	X[16]				X[18]	
Laboratory Evaluations							
Blood Tests[8]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
Urinalysis[9]	X	X[16]	X[16]	X[16]	X[16]	X[16]	

Assessment/Schedule	**Screening**	**Treatment**				**Follow-up**	
Visit	**1**	**2**	**3**	**4**	**5/EOT**	****6/ET**	**7/EOS**
Day	**-28 to -1**	**1***	**(Visit 2 + 4 weeks)**	**(Visit 3 + 4 weeks)**	**(Visit 4 + 4 weeks)**	**(Visit 5 + 4 weeks)**	**(Visit 5 + 8 weeks)**
Visit window		**-**	**+ 7days**	**+ 7days**	**+ 7days**	**± 7days**	**± 7days**
Pregnancy Status[10]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
Virology[11]	X						
Photography[12]		X	X	X	X	X	X
Randomization		X					
CBL-514 or Placebo Administration[17]		X	X	X	X		
Adverse Events[13]		X	X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X[15]

AE: Adverse event; AESI: Adverse event of special interest; Ag/Ab: Antigen/antibody; ALP/ALKP: Alkaline phosphatase; ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; AST: aspartate aminotransferase; β-hCG: Beta human chorionic gonadotropin; BMI: Body mass index; ECG: Electrocardiogram; eGFR: Estimated glomerular filtration rate; EOT: End of treatment: EOS: End of study; ET: Early Termination; FBS: Fasting blood sugar; FSH: Follicle stimulating hormone; GGT: Gamma-glutamyl transferase; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; HBV: Hepatitis B Virus; Hct: Hematocrit; HCV: Hepatitis C Virus; HDL-C: High-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; INR: International normalized ratio; ISR: Injection site reaction; LDL-C: Low-density lipoprotein cholesterol; RBC: Red blood cell; SAE: Serious adverse event; TBIL: Total bilirubin; WBC: White blood cell; WOCBP: Woman of childbearing potential.

* Available measurements of clinical evaluations (physical examinations, vital signs, and ECG) and laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis) within 14 days prior to CBL-514 or Placebo dose can be accepted as the Baseline value and will not necessitate duplicate examinations.
* If study drug dose is within 7 days of Screening pregnancy test, pregnancy test at Visit 2 (Day 1) will not be necessary to assess.
* In cases where more than 1 data is available for a certain evaluation, the latest value prior to the study drug administration will be used as the Baseline value.

** The first follow up visit (Visit 6) should be performed 4 weeks post the final treatment. If treatment is cancelled at Visits 3, 4 or 5 due to the insufficient abdominal fat, it is recommended that first follow up visit is performed on the same day of the treatment cancellation. If not, then +7 days visit window should be utilized to schedule another day to complete the first follow up visit.

[1] Details of concurrent medical conditions, prior surgical procedures and chronic diseases or other significant medical events prior to Screening will be collected. Any other non-significant medical events within 6 months prior to Screening will also be collected. Prior medications include a complete history of previous treatment/medications within 6 months prior to Screening.

[2] Anthropometric parameters include body height, body weight and abdominal skinfold thickness measured by caliper. Body weight will be measured at all visits to calculate the BMI. Body height and abdominal skinfold thickness (by caliper) will be measured at Screening only.

[3] Ultrasound – Thickness of fat will be obtained by ultrasonic measurements across target area. Abdominal ultrasound will be performed within 4 days before Visit 2 (Day 1), Visits 3, 4 and 5; and 4 days before/after the follow-up visits.

[4] A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems and will be performed pre-dose.

[5] On Visit 2 (Day 1), Visit 3, Visit 4, and Visit 5, the injection site assessments will be performed pre-dose and post-dose. Subjects will document any change to the ISRs in between visits in the Subject Diaries.

[6] On Visit 2 (Day 1), Visit 3, Visit 4, and Visit 5, vital signs assessments to be performed pre-dose. Vital sign assessments include temperature, pulse rate, blood pressure, and respiratory rate.

[7] On Visit 2 (Day 1), ECG assessments will be performed pre-dose. ECG to be performed in supine position after at least 5 minutes rest. The following ECG parameters will be recorded: heart rate, RR interval, PR interval, QT interval, and QRS interval.

[8] Blood tests include biochemistry, hematology, and coagulation assessments. Biochemistry assessments include albumin, ALT, AST, ALP, triglyceride, total cholesterol, LDL-C, HDL-C, TBIL, GGT, urea, creatinine, eGFR, HbA1c, FBS, Sodium, Potassium, Bicarbonate, and Chloride. Hematological assessments include Hb, Hct, RBC count, mean corpuscular volume, WBC count, WBC differential, and platelet count. Coagulation assessments include aPTT, Prothrombin time, and INR.

[9] Urinary samples for dipstick will be collected.

[10] Serum β-hCG test will be taken for WOCBP at Screening visit only. FSH test is required for females who are post-menopausal at Screening visit. Urine β-hCG strip test will be taken for WOCBP for other scheduled visits.

[11] Virology tests include HIV/HBV/HCV infection test. Active HIV infection is detected by detectable positive HIV Ag/Ab combo test; HBV: HBsAg; HCV: positive anti-HCV antibody.

[12] On Visit 2 (Day 1), Visit 3, Visit 4, and Visit 5, the photography will be performed pre-dose. The post-dose photography will be performed only when any severe or unusual ISR was observed and assessed by Investigator after IP administration.

[13] The occurring AEs/SAEs (including AESI) will be followed until resolution or the event is considered stable.

[14] On follow-up visits, no subject diary will be provided to subjects and only review and recording of subject dairy entries will be conducted.
[15] Collected only if a medication is related to AEs following the Visit 6
[16] Assessment/collection can be performed on or within 4-days window prior to visit date.
[17] Eligible subjects will be randomly assigned to either the CBL-514 group or placebo group at a ratio of 2:1.
[18] ECG assessment can be performed on or within 4 days before or after Visit 6/ET

9. SELECTION AND WITHDRAWAL OF SUBJECTS

9.1. Subject Inclusion Criteria

To be eligible for this study, a subject must meet ***all*** of the following inclusion criteria:

1. Male or female, aged 18 years to 64 years old (at Screening), inclusive.
2. BMI > 18.5 and < 35 kg/m^2 and body weight ≥ 50 kg at Screening and Day 1.
3. Subject has subcutaneous fat thickness surrounding the center of localized area of treatment.
    a. For Group 1 (320 mg) in Stage 1, thigh subcutaneous fat thickness of at least 1.00 cm (10.0 mm) and up to 4.00 cm (40.0 mm) measured by ultrasound at Screening and Day 1.
    b. For Group 2-4 (480 mg-800 mg) in Stage 1, abdominal subcutaneous fat thickness of at least 2.00 cm (20.0 mm) and up to 5.00 cm (50.0 mm) measured by ultrasound at Screening and Day 1.
    c. For Stage 2, abdominal skinfold thickness of at least 3.00 cm (30.0 mm) and up to 8.00 cm (80.0 mm) by pinch method (measured by calibrated caliper) at Screening.
4. Subject has stable body weight (identified as ≦ 5% weight change per subject report) for at least 3 months before Screening and during the study.
5. Subject who has maintained a stable lifestyle (e.g. exercise, eating patterns, and smoking habit) per subject report for at least 3 months before Screening and during the study.
6. Voluntarily signs the ICF 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.

9.2. Subject Exclusion Criteria

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

1. Female subject 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. Male subject who is not willing to commit to an acceptable contraceptive method. For details on contraception, refer Section 9.3.2.

    Note: Subjects who are not of childbearing potential are not required to use contraception. Females with no childbearing potential are defined as who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are post-menopausal (defined as at least 50 years with ≥ 12 months of amenorrhea with a FSH > 40 IU/L).

2. Subject diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation.
3. Subject has HbA1c ≥ 9%, delayed wound healing, or any diabetic risks which in the opinion of Investigator is inappropriate to participate in the study.
4. Subject has a clinically significant cardiovascular disease and abnormal findings in ECG.
5. Subject with active or prior history of malignancies within 5 years before Screening or being worked-up for a possible malignancy. Except adequately treated basal cell carcinoma of skin and in situ squamous cell carcinoma of skin would be eligible as per Investigator's discretion.
6. Subject with a history of HIV-1infection or subjects with active HIV infection at Screening with positive HIV Ag/Ab combo test.
7. Subject with a history of Trypanophobia, the extreme fear of medical procedures involving injections or needles, or who experience vasovagal syncope and faint or pass out at the sight of blood or a needle.
8. Subject has abnormal skin or local skin conditions at the treatment area, which in the opinion of Investigator is inappropriate to participate in the study, including but not limited to any of the following:
    a. Skin manifestations of a systemic disease,
    b. Any abnormality of the skin or soft tissues of the area to be treated,
    c. Grade III cellulite (Nürnberger and Muller scale, Nürnberger F, 1978) at the area to be treated,
    d. Skin folding and fat folding on abdomen
    e. Sensory loss or dysesthesia in the area to be treated,
    f. Evidence of any cause of enlargement in the area to be treated other than localized abdominal or thigh subcutaneous fat,
    g. Tattoos on the area to be treated.
9. Subject who has undergone the following procedures:
    a. Previous surgery which caused scar tissues on the anticipated treatment area before Screening or during the study, except laparoscopic surgery and surgery which causes very small scar tissues would be eligible as per Investigator's discretion,
    b. Liposuction to the region to be treated before Screening or during the study,
    c. Esthetic procedure e.g. cryolipolysis, ultrasonic lipolysis, LLLT, lipolysis injection to the region to be treated within 12 months before Screening or during the study.
    d. Using medication which is delivered via subcutaneous injection at the treatment area during the study period.
10. Subject is on prescription or OTC weight reduction medication or weight reduction programs within 3 months before Screening or during the study.

11. Subject is undergoing chronic steroid or immunosuppressive therapy, with the exception of oral steroid inhalation indicated for asthma management or topical steroid application for skin conditions that are not directly applied or indirectly affect the treatment area.
12. Requiring continual use of the following therapeutic agents during the study: terfenadine (Teldane), buspirone (Buspar), fexofenadine (Fexotabs, Tefodine, Telfast, Xergic, Allegra, etc.), any medication that is known to strongly inhibit or induce CYP enzymes (please refer to Section 24.1), sensitive CYP substrates or drugs with narrow therapeutic index, in the opinion of the investigator, may affect the evaluation of the study product or place the participant at undue risk.
    If a subject 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 prior to dosing and until 1 day post-dose.
13. Unable to receive local anesthesia (e.g., history of hypersensitivity to lidocaine).
14. Subjects with known allergies or sensitivities to the study treatment or its components.
15. Subjects with liver cirrhosis, with inadequate liver function at Screening defined as AST, ALT, ALKP, TBIL, or GGT > 3.0 × ULN, or with any hepatic medical condition that would interfere with assessment of safety or efficacy or compromise the subject's ability to undergo study procedures or provide informed consent.
16. Subjects with any renal impairment, defined as abnormal serum creatinine, and urea > 1.5 × ULN or eGFR <90 mL/min/1.73 m^2. Subjects who are currently on dialysis should be excluded.

    Subjects 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 subjects may be eligible upon the Investigator's assessment.
17. Use of other investigational drug or device within 12 weeks prior to Screening.

9.3. Prohibitions and Restrictions in the Study

9.3.1. Medication

During the entire duration of the study (from Screening visit to EOS/ET visit) use of following medications, treatment modalities, or diets are prohibited:

a. Use of drugs for weight loss e.g. Orlistat (Xenical), Naltrexone HCl/Bupropion HCl (Contrave), etc.,
b. Use of anticoagulant/antiplatelet therapy or medications or dietary supplements which impede coagulation or platelet aggregation,
c. Any cosmetic or interventional surgery procedures on area to be treated,
d. Use of terfenadine (Teldane), buspirone (Buspar), fexofenadine (Fexotabs, Tefodine, Telfast, Xergic, Allegra, etc.), any medication that is known to strongly inhibit or induce CYP enzymes (please refer to Section 24.1), sensitive CYP substrates or drugs with narrow therapeutic index, in the opinion of the investigator, may affect the evaluation of the study product or place the participant at undue risk,

If a subject 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 prior to dosing and until 1 day post-dose,

e. Use of other investigational drug or device within 4 weeks prior to Screening.
f. Use of medication which is delivered via subcutaneous injection at the treatment area during the study period.

Subjects should be advised not to take any prescription and OTC medications without consulting the Investigator.

9.3.2. Contraception

Highly effective contraceptive methods that can achieve a failure rate of less than 1% per year when used consistently and correctly should be used. The list below is based on the recommendation of the Clinical Trial Facilitation Group (CTFG 2014).

- 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[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomized partner [1,2]
- sexual abstinence[3]
- condom used by male partner during sexual intercourse.

Contraceptive requirements for male subjects with WOCBP partner: A male subject should use condom during heterosexual intercourse and avoid sperm donation from the time of the first dose of study drug, throughout study participation until 12 weeks after the last study drug dose. For the WOCBP partner, contraception recommendations should also be considered.

[1] Contraception methods that in the context of this guidance are considered to have low user dependency.

[2] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.

[3] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, post-ovulation methods) and

withdrawal (coitus interruptus) are not acceptable methods of contraception. This is applicable for both female and male subjects.

9.4. Screen Failures

Screen failures are defined as subjects 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 ensure transparent reporting of screen failure subjects 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. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Re-screening will be allowed once within the recruitment period for the study. Re-screened participants should be assigned a new screening number.

9.5. Subject Replacement

Subjects who are enrolled but who do not receive any IP will be replaced and the replacement subject will receive the same treatment as the subject they are replacing. Subjects who discontinue the study prior to completion of dosing may be replaced at the discretion of the Sponsor.

9.6. Subject Withdrawal Criteria

In accordance with applicable regulations, a subject has the right to withdraw from the study, at any time and for any reason, without prejudice to his (or her) future medical care. If a subject withdraws consent, the date and reason for consent withdrawal should be documented. Subject data will be included in the analysis up to the date of the withdrawal of consent.

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

<u>Stage 1</u>

1. Subject withdraws consent.
2. Between Screening and Day 1, subjects whose overall body weight change of ≥ 3kg.
3. Subject has body weight change ≥ 5 % based on Day 1 body weight.
4. Any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the subject.
5. Subject who cannot complete follow-up visits within 6 weeks post treatment visit.

<u>Stage 2</u>

1. Subject withdraws consent.
2. Subject has body weight change ≥ 3 kg compared to Day 1 body weight during the whole study period.
3. Subject has body weight change ≥ 3 kg during the follow-up period compared to the body weight from the last treatment visit.

4. Any other clinical AE, medical condition, or situation that in the opinion of the Investigator would not be in the best interest of the subject.
5. Subjects has a treatment interval > 6 weeks in length between any of the dosing courses.
6. Subject cannot complete at least the first follow-up visit (Visit 6 / EOT) within 6 weeks post final treatment visit, or cannot complete the second follow-up visit (Visit 7 / EOS) within 10 weeks post final treatment visit.
7. Subject has efficacy related major protocol violation at Day 1 (baseline)

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

If a subject asks or decides to withdraw from the study, the final ET evaluations (as per the schedule of study assessments) will be performed as completely as possible, all efforts will be made to complete and report the observations, especially the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. A clear and concise reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

10. INVESTIGATIONAL PRODUCTS

10.1. CBL-514

CBL-514 is a lipolysis injection product developed by Caliway Biopharmaceuticals Co., Ltd. CBL-514 are constituted by [redacted].

CBL-514 is manufactured in compliance with Good Manufacturing Practice (GMP) regulations.

Table 6: CBL-514 Product Details

Name	**CBL-514**
Dosage Form	Solution for Injection
Dose Concentration per Vial	5 mg/mL
Size of Vial	20 mL/vial
Active Ingredient	[redacted]
Mode of Administration	Subcutaneous injection
Storage	Store at 4°C (39°F), Excursions are permitted between 2°C and 8°C

10.2. Reference/Placebo

The placebo to be used in the study will be commercially available (isotonic) Sodium Chloride for injection (0.9% NaCl). Equivalent volume of Sodium Chloride injection will be administered by subcutaneous injection.

10.3. Dosage and Treatment Periods

10.3.1. Stage 1

A total of 24 subjects enrolled in 4 sequential groups (6 subjects in each group) in Stage 1 of the study, will receive 1 course of allocated CBL-514 dose once. Subjects in Group 1 (320 mg) will receive CBL-514 injections on their thighs, with total allocated dose of IP evenly divided into 2 thighs. Subjects from Group 2 to 4 (480 mg-800 mg) will receive CBL-514 injections on their abdomen with allocated dose of IP.

The dosing scheme is presented in Table 7.

Table 7: Dosing Scheme-Stage 1

Group	**Treatment area**	**CBL-514 Dose Level (mg/cm^2)**	**Injection volume per injection in 4 cm^2 grid space**	**Administration for one dose**			
				No. of Injection	**Total Injection Volume of CBL-514* (mL)**	**Total CBL-514 (mg)**	
1	Thighs	2.0	1.6 mL	40 / 20	64 / 32 (total/ per thigh)	320	[redacted]

Group	Treatment area	CBL-514 Dose Level (mg/cm^2)	Injection volume per injection in 4 cm^2 grid space	Administration for one dose			
				No. of Injection	Total Injection Volume of CBL-514* (mL)	Total CBL-514 (mg)	
				(total/ per thigh)			
2	Abdomen	2.0	1.6 mL	60	96	480	[redacted]
3	Abdomen	2.0	1.6 mL	80	128	640	[redacted]
4	Abdomen	2.0	1.6 mL	100	160	800	[redacted]

*The concentration of CBL-514 is 5 mg/mL

10.3.2. Stage 2

Each enrolled Stage 2 subject will be randomized (2:1) to receive 1 dose level of CBL-514 or placebo. The dose of CBL-514 used in Stage 2 will be set no higher than the highest safe dose from Stage 1. Each subject will receive up to 4 courses of allocated CBL-514 dose or placebo administered in 2.4 mL injections on abdomen, once every 4 weeks. **Subject will receive up to 600 mg dose per treatment with a minimum dose of 300 mg.**

The minimum dose of 300 mg with 25 injections must be administered. It is at the discretion of the Investigator to perform dose adjustment for any dose over the minimum dose administration, which will depend on the level of fat accumulation on subject's abdomen.

The maximum dosing scheme is presented in Table 8

Table 8: Maximum Dosing Scheme-Stage 2

Group	CBL-514 Dose Level (mg/cm^2)	Injection volume per injection in 6.0 cm^2 grid space	Administration for one dose			
			No. of Injection	Total Injection Volume of IP (mL)	Total CBL-514 (mg)	
CBL-514	2.0	2.4 mL	50	120	600	[redacted]
Placebo	-	2.4 mL	50	120	-	-

10.4. Method of Assigning Participants to Treatment

10.4.1. Randomization

Sponsor or designee will manage the randomization of eligible study participants in the study. The randomization schedule will be generated before the start of dosing.

Each subject will be provided with a unique screening number post-documentation of informed consent. Subjects who withdraw from the study, for any reason, without completing all necessary screening assessments will be considered screen failures (see Section 9.4).

Stage 1 of the study will be open label with a total 24 subjects sequentially enrolled in 4 dose groups (6 subjects in each group) to receive one course of allocated CBL-514 dose as presented in Table 7. Once deemed eligible for enrolment in the study, each subject will be assigned a sequential subject number prior to first dosing.

Stage 2 of the study will be a randomized, single-blind, parallel-group. Considering drop-out rates (16% CBL-514 group vs 44% placebo group), approximately 75 subjects are planned to be enrolled and randomized 2:1 (50 subjects in the CBL-514 group and 25 subjects in the placebo group) in order to have a total of at least 56 evaluable subjects in Stage 2 of the study. The dose of CBL-514 used in Stage 2 will be set no higher than the highest safe dose from Stage 1. Once deemed eligible for enrolment in the study, each subject will be assigned a sequential randomization number prior to first dosing.

10.5. Concomitant Medications

All medications*, including OTC medications, and dietary supplements, taken during the 6 months prior to Screening visit will be recorded and reviewed by the Investigator to determine whether the subject is suitable for inclusion in the study.

The use of any other IP or investigational medical device within 4 weeks prior to Screening is prohibited. Additional restrictions relating to prior and concomitant medication use are outlined in Section 9.2 and Section 9.3, respectively.

All medications*, including OTC medications, and dietary supplements, taken by subjects during the course of the study will be recorded in the eCRF and coded using the most current World Health Organization (WHO) drug dictionary available at [redacted] Prior and concomitant medications will be listed by subject and summarized by anatomical therapeutic chemical (ATC) and PT.

*Medications to be reported in the eCRF are concomitant prescription medications, OTC medications, and non-prescription medications. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

A dietary supplement is a product intended for ingestion that contains a “dietary ingredient” intended to add further nutritional value to the diet. A “dietary ingredient” may be one, or any combination, of the substances containing vitamins, minerals, amino acids, or botanical concentrates for use by people to supplement the diet by increasing the total dietary intake.

10.6. Treatment Compliance

Study treatments (CBL-514 or placebo) will be administered at the study site by the designated study staff under guidance of Investigator or designee.

If a subject's study treatment administration and site-related procedures are not conducted as defined in the protocol, the Investigator must make note of ensuring compliance to the protocol for future activities. The date and time of each study treatment administration and accompanying activity will be recorded in the eCRF.

10.7. Blinding

Stage 2 of this study will be conducted in a single-blind manner where the subjects are blinded to treatment but the Investigator, site staff, and the Sponsor, including the Medical Monitor, will be unblinded to treatment assignment to assess safety on an ongoing basis.

Methods of blinding

- Due to the difference in appearance of the placebo and CBL-514, to keep the study single blind, the study needs to create visual barriers to blind subjects. Blinding for subjects will be maintained by physical barrier "sheet" placed over the chest obstructing the subjects own view of their abdomen, using a blindfold/sunglasses to cover subjects' eyes while administration takes place.

If during the study the blind is broken for any reason:

- The reason for unblinding is to be documented in the subject's source documents and case report forms (CRFs). Subjects that were unblinded for any reason during their participation in the study will not be replaced.
- As soon as possible, and without revealing the subject's study treatment assignment (unless important to the safety of participants remaining in the study), the Investigator must notify the Sponsor about unblinding and the reason for unblinding.

11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug

The Sponsor will supply the IP to the investigational site. The IP provided for this study is manufactured under GMP and will be suitable for human use.

11.2. Study Drug Packaging and Labelling

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

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

11.3. Study Drug Storage

Upon receipt, the IP must be stored at 4°C (39°F). Excursions are permitted between 2°C and 8°C. Appropriate storage conditions must be ensured either by controlled room temperature, or by completing a temperature log in accordance with local requirements on a regular basis (e.g., every 30 minutes), showing minimum and maximum temperatures reached over the time interval. In case an out-of-range temperature is noted, the variance must be immediately communicated to the Clinical Project Manager (or designee) and the Sponsor, before further use of the IP. The Clinical Project Manager (or designee) will transmit the out-of-range temperature (copy of the temperature log, duration of the out-of-range temperature, if available) to the Sponsor. Based on reassurance from the Quality Assurance Department, the Sponsor will provide the Clinical Project Manager (or designee) with instructions for the study center regarding use of the IP.

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

11.4. Study Drug 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 administration to subjects, the vials should be warmed up to room temperature. The solution of CBL-514 should be used for injection lipolysis before expiry date.

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

11.5. Administration

To determine the treatment area, Investigators have to determine the location of the Reference point first at the Screening visit. [redacted]

[redacted]

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

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

11.6. Study Drug Accountability

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

11.7. Study Drug Handling and Disposal

On completion of the study, any IP remained 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 site according to the site procedure, 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.

12. STUDY SCHEDULE

A Schedule of Assessments for Stage 1 and Stage 2 of the study are provided in Table 4 and Table 5, respectively.

Where possible, assessments should be conducted in order of least invasive to most invasive.

12.1. Stage 1

12.1.1. Visit 1: Screening (Day -28 to Day -1)

Prior to enrolling in the study, and before performance of any procedures, potential subjects will attend a screening session at which time they 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, subjects will be given time to review study information and ask any questions.

After the consent form is signed, screening assessments will be carried out as follows:

- Review and record subject's demographic details
- Determine subject's eligibility based on inclusion/exclusion criteria
- Review and record subject's demographics, medical history and prior medications (including a complete history of previous, present, and concomitant conditions and treatment/medications within 6 months prior to Screening)
- Collect anthropometric parameters (for Group 1, body height, body weight and thigh circumference will be collected; for Group 2-4, body height and body weight will be collected)
- Perform abdominal or thigh ultrasound
- Perform medical examinations:
  - Physical examination
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation
  - ECG
- Collect blood/urine to perform laboratory evaluations:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (serum)
  - Virology tests.

12.1.2. Visit 2: Treatment/Baseline (Day 1)

12.1.2.1. Before Dosing

Prior to dosing on Day 1, subjects will be sequentially assigned to respective dose group after confirmation of eligibility.

The following assessments will be carried out prior to the administration of IP unless otherwise noted[1]:

- Determine subject's eligibility based on inclusion/exclusion criteria
- Collect anthropometric parameters (for Group 1, body weight and thigh circumference will be collected; for Group 2-4, only body weight will be collected)
- Perform abdominal or thigh ultrasound. Abdominal or thigh ultrasound may be performed up to 4 days before Day 1
- Perform medical examinations:
  - Physical examination
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation
  - ECG
- Collect blood/urine to perform laboratory evaluations:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine)
- Take photographs on the target abdominal or thigh area pre-dose
- Review and record subject's concomitant medications with the reason for administration

[1] Available measurements of clinical evaluations (physical examinations, vital signs, and ECG) and laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis) **within 14 days prior to CBL-514/Placebo dose** can be accepted as the Baseline value and will not necessitate duplicate examinations. If study drug dose is within 7 days of Screening pregnancy test, pregnancy test on Day 1 will not be necessary to assess.
In cases where more than 1 data is available for a certain evaluation, the latest value prior to the study drug administration will be used as the Baseline value.

- Dispense subject diary to record if there are any changes to the injection site/s or any discomforts from Day 1 until last clinic visit or when all ISRs have resolved or stabilized.
- Before the administration of the injections,
  - Subjects will take an analgesic (pain killer) as recommended by the Investigator
  - Wipe subject's abdomen with an antiseptic solution
  - Apply local anesthesia used in local practice to the injection area
  - A cold compress may also be applied before the injection(s) if needed

12.1.2.2. Dosing

CBL-514 will be administered according to the assigned dose level by assigned clinical staff.

12.1.2.3. After Dosing

Subjects will remain at the study site through to the completion of all scheduled post-dose procedures.

The following procedures will be conducted post-dose:

- Apply a cold compress to the treatment area
- Perform medical examinations at the period from 1 hour post-dose to subject leaving the site:
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation
- Take photographs on the target abdominal or thigh area for injection site assessments 1 hour post-dose. Other timepoints can be added to record the ISR at the discretion of the Investigator
- Review and record AEs.
- Pressurize the treatment site with an abdominal binder
- Prescribe analgesic for subjects to bring home as back-up medications
- Provide the Aftercare Procedures and Precautions sheet for subject to bring home.

12.1.3. Visits 3 and 4: Follow-up Period (Week 1/Day 8 [±4 Days] and Week 2/Day 15 [± 4 Days])

Subjects will return to the study site during the follow-up period on Day 8 ± 4 days (Visit 3) and Day 15 ± 4 days (Visit 4).

The following assessments will be carried out on Visit 3 and Visit 4, unless otherwise noted:

- Review Subject diary
- Collect anthropometric parameters (for Group 1, collect body weight only on Visit 3, while collect both body weight and thigh circumference on Visit 4; for Group 2-4, collect only body weight on Visit 3 and 4)
- Perform medical examinations:
  - Physical examination[2]
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation[2]
  - ECG[2]
- Collect blood/urine to perform laboratory evaluations[2]:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine) on Visit 4 only
- Take photographs on the target abdominal or thigh area
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration.

12.1.4. Visit 5: End of Study Visit (Week 4/Day 29 [±4 Days])

Subjects will return to the study site for EOS assessment on Day 29 (±4 days).

The following assessments will be carried out:

- Collect anthropometric parameters (for Group 1, body weight and thigh circumference will be collected; for Group 2-4, only body weight will be collected)
- Perform abdominal or thigh ultrasound. Abdominal or thigh ultrasound may be performed up to 4 days before/after Visit 5
- Perform injection site assessment
- Take photographs on the target abdominal or thigh area for injection site assessments
- Review and record AEs

[2] Assessment/collection can be performed on or within 4-days window prior to visit date.

- Review and record subject's concomitant medications with the reason for administration, only if a medication is related to AEs following the Visit 4.

This visit marks the end of participation in this study.

12.1.5. Early Termination (if applicable)

Subjects who withdraw early from the study will be asked to return to the study site for an EOS assessment at ET visit as soon as possible after withdrawal, no later than 6 weeks from the last dose received.

The following procedures will be conducted:

- Review Subject diary
- Collect anthropometric parameters (for Group 1, body weight and thigh circumference will be collected; for Group 2-4, only body weight will be collected)
- Abdominal or thigh ultrasound will be performed
- Perform medical examinations:
  - Physical examination
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation
  - ECG
- Collect blood/urine to perform laboratory evaluations:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine)
- Take photographs on the target abdominal or thigh area
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration.

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

12.2. Stage 2

12.2.1. Visit 1: Screening (Day -28 to Day -1)

Prior to enrolling in the study, and before performance of any procedures, potential subjects will attend a screening session at which time they 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, subjects will be given time to review study information and ask any questions.

After the consent form is signed, screening assessments will be carried out as follows:

- Determine subject's eligibility based on inclusion/exclusion criteria
- Review and record subject's demographic details
- Review and record subject's medical history and prior medications (including a complete history of previous, present, and concomitant conditions and treatment/medications within 6 months prior to Screening)
- Collect anthropometric parameters (including body height, body weight and abdominal skinfold thickness measured by caliper)
- Perform medical examinations:
  - Physical examination
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation
  - ECG
- Collect blood/urine to perform laboratory evaluations:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (serum)
  - Virology tests

12.2.2. Visit 2: Treatment/Baseline (Day 1)

12.2.2.1. Before Dosing

Prior to dosing on Day 1, subjects will be randomized to respective groups (i.e., CBL-514 group or placebo group) after confirmation of eligibility.

The following assessments will be carried out prior to the administration of IP unless otherwise noted[3]:

- Determine subject's eligibility based on inclusion/exclusion criteria
- Collect anthropometric parameters (including body weight)
- Perform abdominal ultrasound. Abdominal ultrasound may be performed up to 4 days before Day 1
- Perform medical examinations:
  - Physical examination[4]
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation[4]
  - ECG[4]
- Collect blood/urine to perform laboratory evaluations[4]:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine)
- Randomization
- Take photographs on the target abdominal area pre-dose.
- Before the administration of the injections,
  - Subjects will take an analgesic (pain killer) as recommended by the Investigator
  - Wipe subject's abdomen with an antiseptic solution
  - Apply local anesthesia used in local practice to the injection area

[3] Available measurements of clinical evaluations (physical examinations, vital signs, and ECG) and laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis) **within 14 days prior to CBL-514/Placebo dose** can be accepted as the Baseline value and will not necessitate duplicate examinations. If study drug dose is within 7 days of Screening pregnancy test, pregnancy test on Day 1 will not necessitate be necessary to assess.
In cases where more than 1 data is available for a certain evaluation, the latest value prior to the study drug administration will be used as the Baseline value.
[4] Assessment/collection can be performed on or within 4-days window prior to visit date.

– A cold compress may also be applied before the injection(s) if needed

12.2.2.2. Dosing

The dose of CBL-514 used in Stage 2 will be set no higher than the highest safe dose from Stage 1. Subjects will be administered either CBL-514 or the placebo by assigned clinical staff. Subjects will be blinded to IP allocation in Stage 2.

12.2.2.3. After Dosing

Subjects will remain at the study site through to the completion of all scheduled post-dose procedures.

The following procedures will be conducted post-dose:

- Apply a cold compress to the treatment area
- Take photographs on the target abdominal area for injection site assessments only when any severe or unusual ISR was observed and assessed by Investigator after IP administration. Other timepoints can be added to record the ISR at the discretion of the Investigator
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration
- Dispense subject diary to record any changes to the injection site/s or any discomforts after dosing and between visits.
- Pressurize the treatment site with an abdominal binder
- Prescribe analgesic and anti-histamine for subjects to bring home as back-up medications
- Provide the Aftercare Procedures and Precautions sheet for subject to bring home.

12.2.3. Visits 3, 4 and 5 (EOT) Treatment Period (Visit 2+ 4 weeks [+7 Days], Visit 3 + 4 weeks [+7 Days], and Visit 4+ 4 weeks [+7 Days])

12.2.3.1. Before Dosing

The following assessments will be carried out prior to the administration of IP unless otherwise noted:

- Review Subject diary
- Collect anthropometric parameters (including body weight)
- Perform abdominal ultrasound only on Visit 3, 4 and 5. Abdominal ultrasound may be performed up to 4 days before the visits
- Perform medical examinations:

  - Physical examination[5]
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation[5]
- Collect blood/urine to perform laboratory evaluations[5]:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine)
- Take photographs on the target abdominal area pre-dose
- Before the administration of the injections,
  - Subjects will take an analgesic (pain killer) as recommended by the Investigator
  - Wipe subject's abdomen with an antiseptic solution
  - Apply local anesthesia used in local practice to the injection area
  - A cold compress may also be applied before the injection(s) if needed

12.2.3.2. Dosing

CBL-514 will be administered according to the assigned dose group by assigned clinical staff.

12.2.3.3. After Dosing

Subjects will remain in the study site through to the completion of all scheduled post-dose procedures.

The following procedures will be conducted post-dose:

- Apply a cold compress to the treatment area
- Take photographs on the target abdominal area for injection site assessments only when any severe or unusual ISR was observed and assessed by the Investigator after IP administration. Other timepoints can be added to record the ISR at the discretion of the Investigator
- Review and record AEs

[5] Assessment/collection can be performed on or within 4-days window prior to visit date.

- Review and record subject's concomitant medications with the reason for administration
- Dispense subject diary to record any changes to the injection site/s or any discomforts after dosing and between visits.
- Pressurize the treatment site with an abdominal binder
- Prescribe analgesic and anti-histamine for subjects to bring home as back-up medications
- Provide the Aftercare Procedures and Precautions sheet for subject to bring home.

12.2.4. Visits 6: Follow-up Period (Visit 5+ 4 weeks [±7 Days])

Subjects will return to the study site for follow-up period visit 4 weeks after Visit 5 with a visit window of ±7 Days.

The following assessments will be carried out unless otherwise noted:

- Review Subject diary
- Collect anthropometric parameters (including body weight)
- Perform abdominal ultrasound. Abdominal ultrasound may be performed up to 4 days before/after Visit 6
- Satisfaction Questionnaire will be dispensed, and subjects should complete the Questionnaire at this visit. Site will review and record the Questionnaire
- Perform medical examinations:
  - Physical examination[6]
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation[6]
  - ECG[7]
- Collect blood/urine to perform laboratory evaluations[6]:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis

[6] Assessment/collection can be performed on or within 4-days window prior to visit date.
[7] ECG assessment can be performed on or within 4 days before or after visit date.

  - Pregnancy test for WOCBP (urine)
- Take photographs on the target abdominal area
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration.

12.2.5. Visit 7: End of Study Visit (Visit 5+ 8 weeks [±7 Days])

Subjects will return to the study site for an EOS assessment 8 weeks after Visit 5 with a visit window of ±7 days.

The following assessments will be carried out unless otherwise noted:

- Review Subject diary
- Collect anthropometric parameters (including body weight)
- Perform abdominal ultrasound. Abdominal ultrasound may be performed up to 4 days before/after Visit 7
- Perform medical examinations:
  - Perform physical examination[8]
  - Perform injection site assessment
- Take photographs on the target abdominal area
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration, only if a medication is related to AEs following the Visit 6.

This visit marks the end of participation in this study.

12.2.6. Early Termination (if applicable)

Subjects who withdraw early from the study will be asked to return to the study site for an EOS assessment at ET visit as soon as possible after withdrawal, no later than 6 weeks from the last dose received.

The following procedures will be conducted:

- Review Subject diary
- Collect anthropometric parameters (including body weight)
- Perform abdominal ultrasound. Abdominal ultrasound may be performed up to 4 days before/after ET Visit

[8] Assessment/collection can be performed on or within 4-days window prior to visit date.

- Satisfaction Questionnaire will be dispensed, and subjects should complete the Questionnaire at this visit. Site will review and record the Questionnaire
- Perform medical examinations:
  - Physical examination[9]
  - Injection site assessment
  - Vital signs (body temperature, pulse rate, systolic and diastolic BP, and respiratory rate) evaluation[9]
  - ECG[10]
- Collect blood/urine to perform laboratory evaluations[9]:
  - Biochemistry panel
  - Hematology panel
  - Coagulation panel
  - Urinalysis
  - Pregnancy test for WOCBP (urine)
- Take photographs on the target abdominal area
- Review and record AEs
- Review and record subject's concomitant medications with the reason for administration.

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

[9] Assessment/collection can be performed on or within 4-days window prior to visit date.
[10] ECG assessment can be performed on or within 4 days before or after visit date.

13. EFFICACY ASSESSMENTS

Relevant efficacy assessments will be performed by the Investigator or designee in both Stage 1 and Stage 2 of the study, at visits specified in the schedule of events (Table 4 and Table 5, respectively). The assessments will be captured in the eCRF. The assessor who performs the assessments must be a medically qualified physician trained in the assessments. If possible, each subject should have their assessments done by the same assessor throughout the trial. Extra care should be taken to ensure that the same assessor performs the Baseline and post-Baseline assessments (if applicable), where the study endpoint data are collected. Efficacy Parameters to be assessed are:

13.1. Abdominal or Thigh Subcutaneous Fat Thickness

Abdominal or thigh subcutaneous fat thickness in the targeted area, will be measured by ultrasound in both Stage 1 and Stage 2 of the study, at timepoints specified in schedule of assessment Table 4 and Table 5, respectively.

For Stage 2, there will be a total of 4 ultrasound measuring spots within the treatment area (where the area must be injected across the visits). The ultrasound measuring spots will be identified by using the Reference point and laser assisted measurement to ensure the consistency. The subcutaneous fat thickness at the ultrasound measuring point will be measured by ultrasound and will take 3 measurements at each measuring point. Instructions regarding the ultrasound assessment will be provided in a separate Ultrasound Measurement Guidelines manual.

13.2. Abdominal or Thigh Subcutaneous Fat Volume

Abdominal or thigh subcutaneous fat volume over the targeted area, will be measured by ultrasound in both Stage 1 and Stage 2 of the study, at timepoints specified in schedule of assessment Table 4 and Table 5, respectively.

Instructions regarding the ultrasound assessment will be provided in a separate Ultrasound Measurement Guidelines manual.

13.3. The proportion of subjects with a loss of at least 150 mL or 200 mL of subcutaneous fat volume

The proportion of subjects who lose at least 150 mL or 200 mL of subcutaneous fat volume will be compared with placebo to evaluate whether the difference is significant, only in Stage 2 of the study. The abdominal fat volume will be measured by ultrasound as described in Section 13.2.

13.4. 9-point CBL-514 Satisfaction Questionnaire Score

Subject's satisfaction, will be assessed on a 9-point Satisfaction Questionnaire, developed by Caliway Biopharmaceuticals Australia Pty Ltd, only in Stage 2 of the study at timepoints specified in schedule of assessment Table 5.

The satisfaction questionnaire along with instructions regarding completion will be provided separately.

14. ASSESSMENT OF SAFETY

14.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 4 and Table 5). However, if a subject 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

14.1.1. Demographic/Medical History

Medical history (including prior medications), date of birth, age (calculated), sex, ethnicity, and race will be recorded at Screening.

Medical history and prior medications include a complete history of previous, present, and concomitant conditions and treatment/medications within 6 months prior to Screening.

14.1.2. Vital Signs

Vital signs will be measured at the time points specified in the study schedules with subjects resting for at least 5 minutes in a supine position. Vital sign assessments include temperature, pulse rate, blood pressure, and respiratory rate. When the time of vital signs measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible, ensuring the blood draw is within the window specified in the protocol.

Additional vital signs may be performed at other times if deemed necessary.

14.1.3. Anthropometric Parameters

Anthropometric parameters including body height, body weight, abdominal skinfold thickness measured by caliper, and thigh circumference will be recorded at the time points specified in the study schedules. Body height (centimeters) and body weight (kilograms) will be used to calculate BMI. BMI is calculated by dividing the subject's body weight in kilograms by the subject's height in meters squared (kg/m^2). Body weight and height will be obtained with the subject's shoes and jacket or coat removed.

14.1.4. Injection Site Reactions

An examination of the injection site will be performed at the time points specified in the Schedule of Assessments and will include a visual assessment and photography of the skin where the IP will be administered as well as the surrounding area. Examination of the injection site and recording of ISRs may be conducted by the Investigator or designee, so long as the assessment is made consistently. Subject diaries will be provided to the subjects and the subjects will be asked to record if there are any changes to the injection site/s or any discomforts in between visits. ISRs will be recorded as AEs and severity will be assessed according to the CTCAE, version 5.0; please refer Table 9. Severity of AEs related to pain will be assessed by the VAS- Pain Intensity Scale; please refer Figure 2.

All events of ISRs should be monitored until resolution or stabilization.

14.1.5. Physical Examination

Complete physical examinations will be performed by a licensed physician at the time points specified in the study schedules.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.6. Electrocardiogram

An ECG (including parameters: heart rate, RR interval, PR interval, QT interval, QTc interval, and QRS interval) will be taken at the time points delineated in the study schedules. Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with subjects in a supine position. Subjects must be in this position for at least 5 minutes before the reading is taken.

All ECG tracings will be reviewed by the Investigator or designee.

14.1.7. Laboratory Assessments

Safety laboratory tests (hematology, coagulation, biochemistry, urinalysis [dipstick]) will be performed at the time points specified in the study schedules (Table 4 and Table 5). Additional clinical laboratory tests may be performed at other times if deemed necessary based on the subject's clinical condition.

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory.

14.1.7.1. Hematology

Hematology parameters to be tested are:

- Hemoglobin (Hb)
- Hematocrit (Hct)
- Erythrocytes (RBC)
- Platelets (PLAT)
- Leukocytes (white blood cells [WBCs]) with differential (including Eosinophils [ESN], Neutrophils [NEUT], Basophils [BASO], Lymphocytes [LYM], and Monocytes [MONO])
- Mean corpuscular volume.

14.1.7.2. Biochemistry

Biochemistry parameters to be tested are:

- Urea (U)

- Creatinine (CREAT)
- TBIL
- Albumin (ALB)
- ALKP (ALP)
- AST
- ALT
- GGT
- Estimated Glomerular Filtration Rate (eGFR)
- Glycated hemoglobin (HbA1c)
- Fasting Blood Sugar (FBS)
- Sodium (NA)
- Potassium (K)
- Chloride (CL)
- Bicarbonate (BICARB)
- Triglyceride
- Total cholesterol
- LDL-C
- HDL-C.

14.1.7.3. Coagulation

Coagulation parameters to be tested are:

- International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (aPTT)
- Prothrombin Time.

14.1.7.4. Urinalysis

A urinalysis test (dipstick) will be performed for each subject. If clinically significant abnormality is noted for protein, blood, or leukocyte esterase (and at the discretion of the Investigator) a microscopic examination of RBC, WBC, bacteria, and casts will be performed.

14.1.7.5. Viral Serology

HIV Ag/Ab combo test, HBsAg, HBV surface and core antibody test, and HCV antibody testing will be performed at Screening.

14.1.7.6. Pregnancy Testing

All WOCBP will be tested for pregnancy by a serum β-hCG test pregnancy test at Screening visit, and by urine β-hCG strip pregnancy testing for all other scheduled visits. Additional tests will be performed if a subject reports a risk of being pregnant anytime during the study.

14.1.7.7. Follicle Stimulating Hormone Testing

Women not of childbearing potential must be post-menopausal (defined as at least 50 years with cessation of regular menstrual periods for at least 12 months). Post-menopausal status will be confirmed through testing of FSH levels at Screening.

14.1.7.8. Photographs

On Visit 2 (Day 1), Visit 3, Visit 4, and Visit 5, the photography will be performed pre-dose. The post-dose photography will be performed only when any severe or unusual ISR was observed and assessed by the Investigator after IP administration.

Instructions regarding the photographs to be taken will be provided in a separate Image Procedure manual.

14.2. Adverse and Serious Adverse Events

In this study, AEs will be reported for all subjects from the time of consent until the completion of the EOS/ET visit. SAEs will be reported for all subjects (enrolled and not enrolled) from the time of consent. Adverse events reported from the time of consent to pre-dose on Day 1 will be recorded as pre-treatment AEs. Treatment emergent- AEs will be evaluated from the first administration of IP until the EOS/ET visit. Adverse events that are deemed related to treatment and are ongoing 14 days post EOS/ET visit for non-serious AEs and 60 days post EOS/ET visit for serious AEs, the AE outcome will be recorded (e.g. Not Recovered or Recovering) depending on the status and entered on the AE eCRF page (see Section 14.2.1.4).

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

14.2.1. 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 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
- Causality/relation to IP administration procedure
- Action taken regarding IP
- Action taken regarding AE
- Outcome.

14.2.1.1. Severity of an Adverse Event

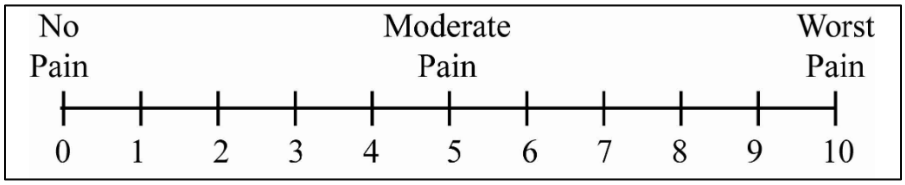
Severity of AEs will be assessed by the Investigator according to the CTCAE, version 5.0; please refer Table 9.

Table 9: CTCAE Severity Grade Description

Grade 1	**Mild**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**	Minimal, local or noninvasive intervention indicated, limiting age-appropriate instrumental activities of daily living*.
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening. Hospitalization or prolongation of hospitalization indicated disabling. limiting self-care activities of daily living**. Note: An experience may be severe but may not be serious, (e.g., severe headache).
Grade 4	**Life-Threatening**	Life-threatening consequences: urgent intervention indicated.
Grade 5	**Fatal**	Death related to AE.
***Note**: A semi-colon indicates 'or' within the description of the grade.* **Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.* ***Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*		

Severity of AEs related to pain will be assessed by the VAS- Pain Intensity Scale; please refer Figure 2.

Figure 2 VAS- Pain Intensity Scale



14.2.1.2. 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 relationship of each AE to IP will be assessed by the Investigator according to categories in Table 10.

Table 10: Criteria for Determination of Adverse Event Relationship to IP

Unrelated	The event is definitely not associated with the IP. Other conditions including concurrent illness, progression or expression of the disease state, or reaction to a concurrent medication explain the reported AE.
Unlikely	The clinical event, including laboratory test abnormality, with a temporal relationship to IP administration based on PK profile in IB which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
Possibly Related	The clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IP administration based on PK profile in IB, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	The clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IP administration based on PK profile in IB, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Definitely Related	The clinical event, including laboratory test abnormality, occurring in a plausible time relationship to IP administration based on PK profile in IB, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.

14.2.1.3. 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 subject then the action taken will be recorded on the AE eCRF page, as one of the following options:

- Dose Reduced
- Drug Interrupted
- Drug Withdrawn
- Not Applicable

- Other.

14.2.1.4. 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.

14.2.2. Definition of Adverse Event of Special Interest

An AESI is any event which may be of medical concern specific to the IP.

Occurrence of any of the below mentioned AESI should trigger a review by the SRC before proceeding with the dose escalation/s (Stage 1) or dosing (Stage 2):

1. Fat atrophy that extends > 2 cm from an injection point or is > 10% of the treated area or is associated with tenderness lasting > 24 hours.
2. Pain limiting self-care ADL lasting more than 72 hours after active intervention (e.g. analgesic).
3. Skin atrophy that extends beyond area of any erythema or induration or is > 10% of the treated area or is associated with tenderness lasting > 24 hours.
4. Any skin hyper or hypopigmentation at the target area and/or the surrounding skin lasting for > 4 weeks.

   * The color change reflecting from the bruising color is not included. The color changes due to deposition or loss of pigment in epidermal tissue is considered as hyper or hypopigmentation.
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.

Above mentioned AESIs are to be reported to the sponsors within 24 hours upon noticed by Investigator or delegates.

14.2.3. 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, that fulfills one or more of the following:

- Results in death
- It is immediately life-threatening
- It requires in-subject 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 subject 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 subject, 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 subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Note: Medical and scientific judgement should be exercised in deciding whether and adverse event/ reaction should be classified as serious in other situations.

14.2.4. Notification of a Serious Adverse Event

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and institutional ethics committees, all SAEs, **must be reported to Sponsor or Sponsor's representative within 24 hours** from the time the site investigational team first become aware of the event.

Initially reporting is achieved by completing an SAE report form and email to the Sponsor or their representative via the assigned project email address, which will be provided upon study setup.

If completion of an SAE form and emailing is not possible, reporting by telephone to Sponsor or their representative is required, and a completed SAE form must be emailed at the first opportunity.

Initial notification of an SAE by telephone to Sponsor must be confirmed in writing 24 hours from the time the site investigational team first becomes aware of the event using the SAE report form as described above.

As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, scanned and emailed to the address at the bottom of the report form.

Withdrawal from the study in the event of an SAE and therapeutic measures taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the subject's medical records and in the eCRF.

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

Abnormal laboratory findings (e.g. biochemistry, hematology, 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 subject 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.

14.2.6. Recording Adverse Events

Adverse events spontaneously reported by the subject 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. Information about AEs and SAEs will be collected from the time of consent until the end of the study. 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 subject to discontinue the study. AEs that occur during the study must be documented in the subject'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 14.2.2. 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 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 subject 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.

14.3. 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 subject 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 subject 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.

14.4. Pregnancy

Pregnancy testing should be performed in all WOCBP throughout the study as per the Schedule of Assessments (Table 4 and Table 5) 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. Male subjects will contact the Investigator immediately if they suspect they may have fathered a child during the study treatment period. When possible, the partner's pregnancies should be followed (to term) to determine the outcome.

If a subject 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 subjects agree to withdraw or terminate the clinical trial, the Investigator should follow-up and document the process and results of all the pregnancies.

If a male subject's female partner becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and sent expeditiously to Sponsor or their representative, irrespective of whether it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to Sponsor or their representative. 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 (including pregnancy of a male participant's

partner), even if no AE has occurred, on a Pregnancy Report Form within 24 hours of the Investigator becoming aware of the pregnancy.

14.5. Dose Limiting Toxicity

No dose limiting toxicities are anticipated.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

Before an investigational site can enter a subject 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 or designee will 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 subject 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 subject'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 subject (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/IEC.

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

15.2. 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.

15.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC 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, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

16. STATISTICS

All data will be handled and processed according to the Sponsor's representative standard operating procedure (SOPs), which are written based on the principles of GCP.

A SAP, containing the detailed planned statistical methods, will be finalized prior to locking of the study database for the final analysis and will form the basis for the programming of the displays and analyses of the final study data. All statistical calculations will be performed using SAS® (SAS Institute Inc., Cary, NC, USA) or similar software. No formal hypothesis testing will be performed, and all analyses will be descriptive in nature.

Statistical methods will be further outlined in the SAP and approved by the Sponsor prior to any analysis. Procedures outlined in the SAP will supersede protocol specified statistical methods in the event of divergence.

Results will be analyzed and presented by stage of the study and dose group.

Descriptive statistics will be used to summarize the safety and efficacy data. No formal hypothesis testing is planned, and dose comparisons will be exploratory in nature. No adjustments will be made for missing or incomplete data, except for missing efficacy data, which may be imputed using multiple imputation.

The Baseline value is defined as the last available result collected/derived prior to the first treatment 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, SD, minimum, median, and maximum for continuous data. Where applicable, 95% CIs for the mean may be presented.

Categorical data will be summarized using counts and percentages. Unless specifically stated otherwise, the denominator for all percentage calculations will be the number of subjects in the treatment group for the specific analysis set. Where applicable, 95% CIs (Clopper-Pearson) may be presented.

All collected and derived data will be listed.

16.1. Analysis Populations

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

16.1.1. Intent-to-treat Population

The ITT population will include all enrolled or randomized subjects who received at least one course of IP treatment.

16.1.2. Safety Population

All subjects who receive at least one confirmed dose of IP will be included in the Safety population. Subjects will be analyzed according to the treatment they actually receive. The safety population will be used for summaries and listings of safety, tolerability, and drug exposure data.

16.1.3. Per Protocol Population

Stage 1

- A subset of ITT
- Subjects without any efficacy related major protocol violations
- Subjects who complete the proposed dosing schedule of study drug and complete all follow-up visits after treatment
- Subjects whose body weight remain stable throughout the study, identified as having body weight change < 3% based on Day 1 body weight.

However, a subject who was discontinued due to an AE, or died before the required exposure could be met, will still be included in this population.

Stage 2

- A subset of ITT
- Subjects without any efficacy related major protocol violations
- Subjects who complete all proposed dosing schedules of study drug and complete 2 follow-up visits after treatment (including the subject who has dose adjustment judged by the Investigator)
- Subjects have all visits of IP administration within 6 weeks
- Subjects whose body weight remain stable throughout the study, identified as having body weight change < 2.5 kg compared to last visit and change of body weight < 3 kg compared to Day 1 body weight
- Subjects whose Visit 6 is performed 3 to 5 weeks post final treatment
- Subjects whose Visit 7 is performed 7 to 9 weeks post final treatment

However, a subject who was discontinued due to an AE, or died before the required exposure could be met, will still be included in this population.

16.2. Safety and Tolerability

Safety and Tolerability assessment is the primary objective of Stage 1 of the study and secondary objective of Stage 2 of the study.

All safety assessments, including AEs, laboratory evaluations, vital signs, ECGs, physical examination, ISR and other safety assessments, will be analyzed using the Safety population.

Safety data from Stage 1 will be reviewed during the SRC meeting before commencement of Stage 2 of the study. A top-level summary of safety data will be submitted to the relevant IEC/IRB for review before proceeding to Stage 2 of the study.

16.2.1. Adverse Event

Adverse events (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 subject AE data

listing, including verbatim term, PT, SOC, treatment, severity, and relationship to IP, will be provided. The number of subjects 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.

16.2.2. 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 by treatment at each protocol specified collection time point.

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

16.2.3. Vital Signs

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

16.2.4. 12-Lead Electrocardiograms

12-lead ECG values will be listed and summarized by treatment by protocol specified collection time point. Observed and change from Baseline will be summarized by treatment at each protocol specified collection time point.

16.2.5. Other Safety Assessments

The following assessments will be listed by subject:

- Medical history
- Prior and concomitant medications
- Pregnancy test/FSH test
- Physical examination
- Serology.

16.3. Efficacy

Efficacy will be analyzed in both Stage 1 and Stage 2 of the study.

16.3.1. Stage 1

Efficacy endpoints to be analyzed in Stage 1 are:

- Reduction of subcutaneous fat thickness as measured by ultrasound compared with Baseline

- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline.

*Note: no efficacy endpoints will be assessed for Group 1 of Stage 1 study.

The reduction of subcutaneous fat thickness and subcutaneous fat volume over the treated area will be summarized with descriptive statistics. An estimate of the 95% CI for the mean reduction in subcutaneous fat thickness and corresponding p-value will also be provided.

The analysis set for the primary efficacy analysis is the ITT population. The primary analysis will be repeated using the PP population, as relevant. Exploratory analyses may be performed to assess differences between the dose levels. Full details of all exploratory analyses will be provided in the SAP.

16.3.2. Stage 2

Primary efficacy endpoints to be analyzed in Stage 2 are:

- The proportion of subjects who lose at least 150 mL of subcutaneous fat as measured by ultrasound compared with placebo

Secondary efficacy endpoints to be analyzed in Stage 2 are:

- The proportion of subjects who lose at least 200 mL of subcutaneous fat as measured by ultrasound compared with placebo
- Number of treatments required to first occurrence of reducing at least 150 mL of subcutaneous fat volume over the treated area as measured by ultrasound in CBL-514 group
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with placebo
- Reduction of subcutaneous fat volume over the treated area as measured by ultrasound compared with Baseline

For the primary endpoint, the proportion of subjects who lose at least 150 mL of subcutaneous fat will be summarized for CBL-514 and placebo, respectively, along with their 95% confidence intervals.

The analysis set for the primary efficacy endpoint is the ITT population. The primary analysis will be repeated using the PP population, as relevant. Exploratory analyses may be performed to assess differences between the dose levels.

All analyses will be performed without adjustment for multiple endpoints.

Full details of all efficacy analyses will be provided in the SAP.

17. ETHICS

17.1. 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/IEC as appropriate. The Investigator must submit written approval to the Sponsor before they can enroll any subject into the study.

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

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

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

17.2. 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.

17.3. Written Informed Consent

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

The subject’s signed and dated informed consent must be obtained before conducting any study procedures. The subjects 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 subject’s medical records, as required, and the ICF will be signed and personally dated by the subject 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 subject or legal representative. The date that informed consent was signed will be recorded on the eCRF.

17.4. Data Protection

Subjects 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. Subjects will also be informed that a study report will be prepared and may be submitted to regulatory authorities and for publication. However, subjects will be identified in such reports only by study identification number, gender, and age. All subject data will be held in strict confidence.

18. DATA HANDLING AND RECORDKEEPING

18.1. 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, subject charts and study source documents, and other records relative to study conduct.

18.2. 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 subject'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/IEC 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 (as required in Australia).

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.

18.3. 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 subjects or Investigator(s).

19. PUBLICATION POLICY

19.1. Publication of Results

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. Subject confidentiality will be maintained by referring to individual subjects 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 Australian New Zealand Clinical Trials Registry as required by legal agreement, local law or regulation.

19.2. Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from site staff and the local IRB/IEC. Study documents provided by the Sponsor (protocols, IBs, eCRFs, etc.) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

The Investigator must ensure that the subject's anonymity is also maintained. Subjects should only be identified by their initials and a subject study number on the eCRFs and other source documents. Other study-related documents (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

20. QUALITY CONTROL AND QUALITY ASSURANCE

20.1. Compliance with Good Clinical Practice

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Please see Section 15.3 for more details regarding the audit process.

This study will be conducted in compliance with IRB/IEC and ICH GCP Guidelines; Title 21 Part 56 of the US Code of Federal Regulations (CFR) relating to IRBs/IECs and GCP as described in the US FDA CFR (21 CFR § 50, 56, 312; applicable ICH guidelines regarding clinical safety data management (E2A, E2B[R3]); and with ICH guidelines regarding scientific integrity (E4, E8, E9, and E10). In addition, this study will adhere to all local regulatory requirements, and requirements for data protection.

20.2. 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

21. CLINICAL STUDY REPORT

A clinical study report (CSR) will be prepared with reference to the Tripartite Harmonised ICH Guideline: Structure and Content of Clinical Study Reports E3 (November 1995) to include:

- Details of where the study was carried out
- Dates of the start and completion of each period of the study
- Details of the IP and a statement of production will be provided by the Sponsor
- A statement confirming that the applicable IRB/IEC gave written approval for the study in accordance with local regulations
- A demographic listing for all subjects
- A list of all AEs according to IP
- Details of any occurrences which may be of significance to the study outcome
- Details of all operations, calculations and transformations performed on the reported data
- The SAP and report will be produced by the Sponsor, or their agents, and will be incorporated into the final report

- A scientific interpretation of the results
- A description of the study methods used.

Consideration will be given to any comments on a draft report. The report will incorporate the analytical and statistical results and methods produced by the Sponsor or their agents. A final report will be prepared to contain all those sections in the draft and a statement of compliance covering all the areas of the study conducted at the investigational site and the report, with GCP. The report will be issued under the Sponsor's responsibility.

Where required by the applicable regulatory requirements, an Investigator signatory will be identified for the approval of the CSR. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports, and will have the opportunity to review complete study results. The Sponsor will also provide the Investigator with the full summary of study results.

22. SPONSOR AND INVESTIGATOR OBLIGATIONS

22.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify or alter this protocol without the agreement of the other. All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IRB/IEC for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter.

22.2. 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/IEC (if required) and included in the CSR.

23. LIST OF REFERENCES

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3. Atiyeh BS, Ibrahim AE, Dibo SA. Cosmetic mesotherapy: between scientific evidence, science fiction, and lucrative business. Aesthetic Plast Surg. 2008;32(6):842-849.
4. Duncan D, Rotunda AM. Injectable therapies for localized fat loss: state of the art. Clin Plast Surg. 2011;38(3):489-vii.
5. Friedmann DP. A review of the aesthetic treatment of abdominal subcutaneous adipose tissue: background, implications, and therapeutic options. Dermatologic Surgery : Official Publication for American Society for Dermatologic Surgery [et al.]. 2015 Jan;41(1):18-34.
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7. Jalian HR, Avram MM. Body contouring: the skinny on noninvasive fat removal. Semin Cutan Med Surg. 2012;31(2):121-125.
8. Kennedy J, Verne S, Griffith R, Falto-Aizpurua L, Nouri K. Non-invasive subcutaneous fat reduction: a review. J Eur Acad Dermatol Venereol. 2015;29(9):1679-1688.
9. Nestor MS, Newburger J, Zarraga MB. Body contouring using 635-nm low level laser therapy. Semin Cutan Med Surg. 2013;32(1):35-40.
10. Nürnberger F, Müller G. So-called cellulite: an invented disease. J Dermatol Surg Oncol. 1978;4(3):221-229.
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24. APPENDIX

24.1. Appendix I: Reference List of Prohibited Substances (CYP inhibitors and inducers only)

The following table (not exhaustive) provides a list of drugs, herbal products and foods that are CYP inhibitors or inducers for reference only. Any questions or concerns should be referred to the Sponsor or Investigator for review.

CYP3A4 Inhibitors	Drugs	amprenavir, aprepitant, atazanavir, boceprevir, ciprofloxacin, clarithromycin, cobicistat, conivaptan, crizotinib, cyclosporine, danoprevir, darunavir, diltiazem, dronedarone, elvitegravir, erythromycin, faldaprevir, fluconazole, idelalisib, imatinib, indinavir, isavuconazole, itraconazole, ketoconazole, mibefradil, nefazodone, nelfinavir, netupitant, nilotinib, posaconazole, ribociclib, ritonavir, saquinavir, telaprevir, telithromycin, tofisopam, troleandomycin, verapamil, voriconazole
	Herbals and Foods	grapefruit juice, *Schisandra sphenanthera* extract
CYP3A4 Inducers	Drugs	bosentan, carbamazepine, dabrafenib, efavirenz, enzalutamide, etravirine, genistein, lopinavir, lumacaftor, mitotane, modafinil, nafcillin, phenobarbital, phenytoin, rifabutin, rifampicin[rifampin], telotristat, thoridazine
	Herbals and Foods	St. John's wort
CYP2D6 Inhibitors	Drugs	• Amiodarone • Celecoxib • Chloroquine • Chlorpromazine • Cimetidine • Citalopram • Clomipramine • Codeine • Delavirdine • Desipramine • Dextropropoxyphene • Diltiazem • Doxorubicin • Entacapone (high dose) • Fluoxetine • Fluphenazine • Fluvaxamine • Haloperidol • Labetalol • Lobeline

		• Lomustine • Methadone • Mibefradil • Moclobemide • Nortuloxeline • Paroxetine • Perphenazine • Propafenone • Quinacrine • Quinidine • Ranitidine (ranitidine, Zantac) • Risperidone (weak) • Ritonavir • Serindole • Sertraline (weak) • Thioridazine • Valproic acid • Venlafaxine (weak) • Vinblastine • Vincristine • Vinorelbine • Yohimbine
CYP2D6 inducer		Dexamethasone • Rifampin

Prohibited substances (CYP inhibitors and inducers only) compiled from multiple sources, including:

1. FDA DDI Index Inhibitors and Inducers (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
2. Flockhart Table at Indiana University (https://drug-interactions.medicine.iu.edu/Home.aspx)
3. UW DIDB (https://www.druginteractionsolutions.org/solutions/drug-interaction-database/)
4. Prescriber's Information for FDA approved products