A PHASE 2 STUDY TO EVALUATE THE PHARMACOKINETIC PROFILE OF CBL-514 INJECTION IN HEALTHY VOLUNTEERS

Protocol Number: CBL-0203

Authors: [redacted]

Development Phase: Phase 2

Document Version: Protocol Version 1.0 dated 18 October 2021

PROTOCOL AUTHORIZATION

Title: A Phase 2 Study to Evaluate the Pharmacokinetic Profile of CBL-514 Injection in Healthy Volunteers

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

[redacted] 2021.10.18

Signature Date

[redacted]

General Manager, Caliway Biopharmaceuticals Co., Ltd.

INVESTIGATOR'S AGREEMENT

Title: A Phase 2 Study to Evaluate the Pharmacokinetic Profile of CBL-514 Injection in Healthy Volunteers

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/Independent Ethics Committee (IRB/IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB/IEC, 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.

_____

Investigational Site

_____

Printed name of Investigator

_____

Signature of Investigator

_____

Date

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Clinical Study Leader	[redacted]	Caliway Biopharmaceutials Co., Ltd. 32-2F, No. 99, Sec. 1, Xintai 5th Rd., Xizhi Dist. New Taipei City 221, Taiwan Email: [redacted]
Medical Monitor / 24-hour Emergency Contact	[redacted]	[redacted]

2. SYNOPSIS

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

Name of Investigational Product:
CBL-514

Name of Active Ingredient:
Curcumin and *trans*-resveratrol

Protocol Number:
CBL-0203

Title of Study:
A Phase 2 Study to Evaluate the Pharmacokinetic Profile of CBL-514 Injection in Healthy Volunteers

Phase of Development:
Phase 2

Objectives:

Primary:

- To evaluate the pharmacokinetics (PK) profile of the components of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat.

Secondary:

- To identify and assess the metabolites of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat.
- To evaluate safety and tolerability of CBL-514 administered into subcutaneous fat.

Methodology:

This is a Phase 2 study to evaluate the safety, tolerability, PK and metabolite profile of CBL-514 injection at the maximal use dosage.

This Phase 2 study has an open-label and single course design. A total of 10 adult participants, composed of 5 females and 5 males, will be enrolled in a single cohort. Each participant will receive a single course of treatment with CBL-514 800 mg on the abdomen (administered as multiple subcutaneous injections) on Day 1 only.

The dosing scheme is presented in the table below.

Table S1: Dosing Scheme

Treatment Area	Dose level (mg/cm^2)	Injection volume per 7.5 cm^2 grid (mL)	Administration			
			No. of injections	Total injection volume (mL)	Total CBL-514 (mg)	
Abdomen	2.0	[redacted]	[redacted]	160	800	Curcumin [redacted]
						Resveratrol [redacted]

Note: The concentration of CBL-514 is [redacted] mL.

In accordance with the maximal use of CBL-514, [redacted] will be administered to each participant in order to reach the required injection dosage of 800 mg.

Oral analgesia as per standard of care will be administered to participants approximately 1 hour prior to IP administration. Topical anesthesia cream will be applied to the treatment area, followed by local anesthesia injection, both as per standard of care. If needed, participants may undergo ice compress immediately prior to IP injection. The IP administration should be completed within 60 minutes.

Participants will remain in the clinic for at least 24 hours after dosing. During this time, blood samples will be collected to determine the PK and metabolites profile of curcumin and resveratrol. PK samples will be collected from all 10 participants. Of these 10 participants, 6 participants (the first 3 females and the first 3 males enrolled) will have additional samples collected for metabolite assessment.

Prior to discharge on Day 2, at the discretion of Investigator, participants may be prescribed analgesics and/or antihistamines to treat injection site reactions.

Follow-up will be performed at Week 2 and Week 4 to assess safety.

An Early Termination visit will be planned for any participant who receives treatment and is withdrawn from the study earlier than scheduled.

Participants who cannot meet the dosing compliance specified in Section 10.5 will be withdrawn and will not continue the collection of PK samples post-dose. Safety assessment post-dose on Day 1 will be completed before discharge and an Early Termination visit will be planned.

Number of Participants:

10 (5 females and 5 males).

Inclusion Criteria:

A participant can participate in the study only if all the following criteria are met:

1. Male/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. Participant has sufficient subcutaneous fat thickness of at least 3.00 cm (30.0 mm) measured by caliper skinfold method surrounding the center of localized area of treatment as well as the left and right edges of treatment area at Screening and Day 1.
4. 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, including food and drink restrictions.

Exclusion Criteria:

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

1. Women of childbearing potential (WOCBP) who are not willing to commit to an acceptable contraceptive regimen from the time of Screening and throughout study participation until 90 days after the last IP dose, or who are currently pregnant or lactating. Male participants who are not willing to commit to an acceptable contraceptive method. For details on contraception, refer to Section 9.3.3. Female participants who are not WOCBP are not required to use contraception.

* Not WOCBP is defined as females who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are postmenopausal (defined as at least 50 years, with ≥ 12 months of amenorrhea) with a follicle-stimulating hormone (FSH) > 40 IU/L prior to Screening.

2. Participant diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation.
3. Participant 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. Participant has a clinically significant cardiovascular disease and clinically significant abnormal findings in electrocardiogram (ECG).
5. Participant 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. Participant with a history of human immunodeficiency virus (HIV)-1 infection, or participants with active HIV infection at Screening with positive HIV antigen/antibody (Ag/Ab) combo test.
7. Participants with any hepatic medical condition that, in the opinion of the Investigator, would compromise the participant's ability to undergo study procedures and/or interfere with the assessment of the obtained data.
8. Participants 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.
9. Participant 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. Cicatricial tissue or any abnormality of the skin or soft tissues on the anticipated treatment area,
    c. Grade III cellulite (Nürnberger and Muller scale, Nürnberger F, 1978) at the area to be treated,
    d. Skin folding on treatment area when the participant is in the supine position,
    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 subcutaneous fat,
    g. Tattoos on the area to be treated.
10. Participant who has 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, low-level laser therapy (LLLT), lipolysis injection to the region to be treated within 12 months before Screening or during the study.

11. Participant is undergoing chronic systemic steroid or immunosuppressive therapy.
12. Requiring continual use of the following therapeutic agents during the study: terfenadine, buspirone, fexofenadine, any medication that is known to strongly inhibit or induce CYP enzymes (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 participant needs to use the above-mentioned therapeutic agents during the study for any reason, these therapeutic agents should not be used for at least 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. Participants with known allergies or sensitivities to the IP or its components.
15. Participants with liver cirrhosis or with inadequate liver function at Screening defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBIL), or gamma-glutamyl transferase (GGT) > 3.0 × upper limit of normal (ULN).
16. Participants with any renal impairment, defined as abnormal serum creatinine, and urea > 1.5 × ULN or estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2. Participants who are currently on dialysis should be excluded.

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

Withdrawal criteria:

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

- Participant withdraws consent,
- Participant cannot meet the dosing compliance specified in Section 10.5,
- Any other clinical adverse event (AE), medical condition, or situation arises, that in the opinion of the Investigator it would not be in the best interest of the participant to continue participation.

Investigational Product, Dosage and Mode of Administration:

Table S2: CBL-514 Product Details

Name	CBL-514
Active Ingredients	Curcumin and *trans*-resveratrol
Dosage form	Subcutaneous Injection, [redacted]/mL of CBL-514, 20 mL/vial
Pharmacological category	D11AX other dermatological

Duration of Treatment:

The Screening period is 28 days (Day –28 to Day 1).

Each participant will participate in the study for approximately 4 weeks, including an Admission/Baseline visit on Day 1 with an overnight stay until Day 2, and 2 Follow-up visits (2 weeks [in-clinic] and 4 weeks [telephone] post treatment).

Duration of study participation is defined as the period between the day the participant provides written consent and 28 days after dose administration, or until all study required examinations have been completed, whichever is longer or applicable.

Criteria for Evaluation:

Pharmacokinetics:

- The primary PK endpoint is to evaluate the PK of the components of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat. PK parameters following a single course of administration of CBL-514 will include, but are not limited to the following:
  - Maximum analyte concentration (C_{max})
  - Time to C_{max} (t_{max})
  - Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-t})
  - Area under the concentration-time curve from time 0 to 24 hours post-dose (AUC_{024hr})
  - Area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf})
  - Elimination half-life ($t_{½}$)
  - Apparent total plasma clearance (CL/F)
  - Apparent terminal volume of distribution (Vz/F)
- The secondary PK endpoint is to identify and characterize the metabolites of CBL-514 following administration of CBL-514 into subcutaneous fat.

Blood samples for PK and metabolite analysis will be collected at the following time points on Day 1 and Day 2: pre-dose (within 30 minutes prior to scheduled dosing), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), 5 hours (± 10 minutes), 6 hours (± 10 minutes), 7 hours (± 10 minutes), 8 hours (± 10 minutes), 10 hours (± 10 minutes), 12 hours (± 10 minutes), 18 hours (± 10 minutes), and 24 hours (± 10 minutes) post-dose (from the start of CBL-514 administration).

Safety:

- The safety endpoints are the safety and tolerability following a single subcutaneous dose of CBL-514 as assessed by recording of treatment-emergent adverse events (TEAEs), laboratory assessments, vital signs, ECGs, and physical examinations.

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 PK data. No adjustments will be made for missing or incomplete data.

Analysis Populations

PK Population:

The PK Population will consist of all participants who receive any amount of IP and have sufficiently evaluable concentration-time profiles of plasma curcumin and/or resveratrol to allow determination of at least one PK parameter among C_{max}, t_{max}, and AUC_{0-24hr}. An evaluable PK profile will be determined at the discretion of the pharmacokineticist following examination of participants with

dosing or protocol deviations that could potentially affect the PK profile. The PK Population determination will be done by the study pharmacokineticist post database lock.

The PK Population will be used for PK analyses and the summaries of all PK data. Any participant or data excluded from the analysis will be identified, along with their reason for exclusion, in the clinical study report (CSR).

Metabolites Population:

The Metabolites Population will consist of all participants who receive any amount of IP and have at least one quantifiable concentration of any identified metabolite(s) of curcumin and/or resveratrol.

The Metabolite Population will be used for presenting individual and summary concentrations only without PK analysis and/or PK parameters. Any participant or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

Safety Population:

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

Pharmacokinetics Assessment

Plasma concentrations and derived PK parameters for curcumin and resveratrol will be summarized descriptively. Any identified metabolite(s) concentrations of curcumin and/or resveratrol will only be presented for listings and summary without PK analysis and/or PK parameters.

Safety Assessment

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

AEs will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the start of the study. A by-participant AE data listing, including verbatim term, Preferred Term (PT), System Organ Class (SOC), treatment, severity, and relationship to IP, will be provided. The number of participants experiencing TEAEs and number of individual TEAEs will be summarized by SOC and PT. TEAEs will also be summarized by severity and by relationship to the IP.

Observed values and changes from Baseline in clinical laboratory tests and vital signs will be summarized using descriptive statistics. Physical examination findings and ECGs will also be summarized descriptively.

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
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASO	Basophils
BMI	Body mass index
CI	Confidence interval
CREAT	Creatinine
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	estimated glomerular filtration rate
EOS	End of Study
ESN	Eosinophils
ET	Early termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen

Abbreviation or Specialist Term	Explanation
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIFU	High intensity focused ultrasound
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
ISR	Injection site reaction
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDL-C	Low-density lipoprotein cholesterol
LLLT	Low-level laser therapy
LYM	Lymphocytes
MCHC	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
MONO	Monocytes
NEUT	Neutrophils
NHMRC	National Health and Medical Research Council
OTC	Over-the-counter
PK	Pharmacokinetics
PLAT	Platelets
PT	Preferred term
RBC	Red blood cells/ erythrocytes
SAD	Single ascending dose

Abbreviation or Specialist Term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
U	Urea
ULN	Upper limit of normal
US	United States
WBC	White blood cells
WHO	World Health Organization
WOCBP	Woman of childbearing potential
β-hCG	Beta human chorionic gonadotropin

Definitions of the pharmacokinetic parameters to be determined are provided in Table 10.

5. FACILITIES AND PERSONNEL

Table 3: Facilities and Personnel

Sponsor	Caliway Biopharmaceuticals Australia Pty Ltd. 58 Gipps Street, Collingwood, VIC 3066, Australia Email: cr@caliway.com.tw
Local Medical Monitor	To be confirmed
Biostatistical Analysis	To be confirmed
Data Management / Project Management / Monitoring	To be confirmed

6. BACKGROUND AND INTRODUCTION

6.1. Introduction

The focus on body aesthetics and appearance continues to influence the treatment-seeking behavior of many people in 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 2014; Kennedy 2015).

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

Commonly used treatment options for abdominal and thigh subcutaneous fat have been limited to invasive surgical or non-surgical procedures. Lipoplasty was the most popular procedure performed by American Society of Aesthetic Plastic Surgery members in 2020, with 296,601 procedures performed (ASAPS 2020). 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 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, high intensity focused ultrasound (HIFU), cryolipolysis or low-level laser therapy (LLLT) (Friedmann 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 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, deoxycholate alone or combinations including other drugs or products such as vitamins, minerals, and herbal extracts may be used (Rotunda 2006; Atiyeh 2008). However, warning letters were issued by the Food and Drug Administration (FDA) to medical spas offering mesotherapy for unfounded claims of efficacy (Atiyeh 2008; Duncan 2011). There were also numerous reports of significant adverse events

(AEs) (e.g., skin necrosis, infections, etc.) due to unregulated mesotherapy (Atiyeh 2008, Duncan 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.

CBL-514 injection (CBL-514), is a new injection for lipolysis product developed by Caliway Biopharmaceuticals Co., Ltd. The product is supplied in a 20 mL glass vial with a stopper. Each milliliter of CBL-514 contains [redacted] the drug substance, the CBL-514 powder, with [redacted] curcumin (CAS number: 458-37-7) and [redacted] *trans*-resveratrol (CAS number: 501-36-0) 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 Investigator's Brochure (IB).

6.2.2. Clinical Studies

The safety and tolerability of injection lipolysis with CBL-514, pharmacokinetic (PK) profile of and preliminary efficacy of repeated doses of CBL-514 in reducing abdominal subcutaneous fat at the target area has been evaluated in a first-in-human Phase 1/2a study (CBL-16001) in Australia.

In the Phase 1 component of CBL-16001, CBL-514 was assessed for safety and tolerability, and the PK profile was evaluated. The study was conducted with a single ascending dose (SAD) design, in 9 sequential cohorts (Cohorts 1 to 9). The CBL-514 dose levels assessed were 2, 10, and 20 mg at 0.5 mg/cm^2; 40 mg at 1.0 mg/cm^2; and 40, 80, 160, 240, and 320 mg at 2.0 mg/cm^2. 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 participants.

In the Phase 2a component of the CBL-16001 study, the safety and efficacy of multiple injections of CBL-514 for reducing abdominal subcutaneous fat was assessed. There were 3 parallel treatment groups. The CBL-514 dose levels assessed were CBL-514 180 mg at 1.2 mg/cm^2, 240 mg at 1.6 mg/cm^2, and 300 mg at 2.0 mg/cm^2. Each enrolled Phase 2a participant received 4 courses of study drug, 1 course of CBL-514 every 2 weeks, over a period of 6 weeks.

6.2.2.1. Safety and Tolerability

Overall, single doses of CBL-514 were well tolerated through the ascending dose escalation scheme from 2 to 320 mg in the Phase 1 portion of CBL-16001 study. The results for 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

were no systemic treatment-emergent AEs (TEAEs) from CBL-514, the most frequent TEAEs were injection site reactions (ISRs). In Cohorts 1 to 5, the drug-related ISRs were warmth (81%), erythema (75%), bruising (63%), yellow discoloration (38%), tenderness (31%), and pruritus (25%), with higher incidence on the treatment area. All drug-related ISRs were graded as mild and most resolved within 8 days; bruising resolved within the 28-day follow-up period. There was no apparent difference in severity or duration of common ISRs with dose escalation.

Within the first 5 cohorts (Cohort 1 to 5) which received both placebo and CBL-514, 50% of participants in the pooled placebo group and 81% of participants in the pooled CBL-514 group experienced at least 1 ISR. In Cohorts 6 to 9, the most frequently occurring CBL-514 related ISRs were erythema, warmth, bruising, swelling, and yellow discoloration (reported for 80% to 99% of participants), tenderness and pruritus (reported for 60% to 79% of participants), and pain (reported for 50% of participants). All CBL-514-related ISRs were graded as mild to moderate. Among these ISRs, yellow discoloration was caused by the natural yellow pigment, curcumin, an active component of CBL-514. In all cases, the yellow discoloration faded away and completely disappeared from the skin within 8 days (for further details, refer to the IB).

Overall, CBL-514 appeared to be safe and well tolerated when administered as multiple doses at 180 to 300 mg in the Phase 2 portion of the CBL-16001 study. The most commonly reported treatment-related TEAEs were injection site bruising (100%), injection site erythema (100%), injection site pain (100%), injection site swelling (100%), injection site pruritus (95.3%), injection site warmth (90.7%), injection site discoloration (79.1%), and injection site induration (46.5%). The majority of TEAEs were either mild or moderate in severity. There were no apparent differences between the different CBL-514 dosing groups in terms of study treatment-related TEAEs.

6.2.2.2. Pharmacokinetics

PK data were collected in the Phase 1 portion the CBL-16001 study for participants in Cohorts 3 through Cohort 9 (single doses of CBL-514, from 20 to 320 mg).

Curcumin median t_{max} ranged from approximately 2 to 5 hours while geometric mean curcumin $t_{1/2}$, when estimable, ranged from approximately 2 to 3.5 hours. Curcumin exposure (C_{max} and $AUC_{0\text{-last}}$) increased in an approximately dose proportional manner with an 8-fold increase in CBL-514 dose from 20 to 160 mg. Following the 2 highest doses, which represent a 12- and 16-fold increase in the dose from 20 mg, geometric C_{max} increased approximately 15- and 18-fold. The geometric mean $AUC_{0\text{-last}}$ increased on average approximately 16-fold, following each of the top 2 doses. Based on the statistical assessment of curcumin dose proportionality, the increase in curcumin exposure was proportional to curcumin dose across the dose range studied. The 90% confidence interval (CI) for the slope of the relationship between curcumin dose and exposure included 1 for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$.

Resveratrol median t_{max} ranged from 4 to 5 hours while geometric mean resveratrol $t_{1/2}$ ranged from 3 to 5 hours. Resveratrol exposure (C_{max} and $AUC_{0\text{-last}}$) increased in an approximately dose proportional manner with an 8-fold increase in CBL-514 dose from 20 to 160 mg. Exposure to resveratrol increased following the administration of 240 and 320 mg CBL-514 doses with exposure tending to plateau from 240 to 320 mg of CBL-514. Following the 2 highest doses, which represent a 12- and 16-fold increase in dose from 20 mg, the increase in geometric mean resveratrol C_{max} was approximately 10-fold for both doses while the increase in geometric mean

resveratrol $AUC_{0\text{-last}}$ was approximately 14-fold for both doses. Based on the statistical assessment of resveratrol dose proportionality, the increase in resveratrol C_{max} was slightly less than proportional to resveratrol dose while resveratrol $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ was proportional to resveratrol dose. The upper bound of the 90% CI for the slope of the relationship between resveratrol C_{max} and resveratrol dose did not include 1 while the 90% CI for the slope of the relationship between resveratrol $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ and resveratrol dose included 1.

6.2.2.3. Efficacy

Four courses of CBL-514 injections at doses of 240 mg and 300 mg showed statistically significant decreases in fat volume and fat thickness compared to Baseline ($p<0.001$) in the Phase 2 portion of the CBL-16001 study. There was an apparent dose-response effect observed, with CBL-514 injection at multiple doses of 300 mg yielding statistically significant reductions from Baseline in fat volume compared to the lowest dose group.

6.3. Dosage Rationale

In order to cater to a greater range of body shapes and/or levels of fat accumulation, higher doses of CBL-514 may be required to provide effective treatment. On the basis of the favorable safety and efficacy profile demonstrated in the CBL-16001 study, further studies at higher doses are planned to evaluate the efficacy, safety, tolerability and PK of CBL-514 injection for reducing abdominal and thigh subcutaneous fat.

An ongoing Phase 2 study (protocol number: CBL-0202) has an integrated design consisting of a SAD part in Stage 1, followed by a parallel-arm, placebo-controlled design in Stage 2. The doses being evaluated in Stage 1 are 320, 480, 640, and 800 mg at 2.0 mg/cm^2. In Stage 2, the planned minimum dose is 300 mg and the planned maximum dose is 600 mg. The dose adjustment will depend on the level of fat accumulation on a participant's abdomen at the discretion of the Investigator. The dose for Stage 2 is to be confirmed or adjusted after an interim safety report has been reviewed by the Institutional Review Board/Independent Ethics Committee (IRB/IEC).

The PK profile of curcumin and resveratrol has been investigated following subcutaneous administration CBL-514 at doses up to 320 mg. The present study, CBL-0203, is intended to evaluate the PK profile of curcumin and resveratrol at the maximal CBL-514 dose. The maximal dose is anticipated to be 800 mg at 2.0 mg/cm^2, based on the emerging safety profile in Stage 1 of the ongoing CBL-0202 study. The dose for CBL-0203 is to be confirmed or adjusted after an interim safety report from CBL-0202 has been reviewed by the IRB/IEC.

6.4. Participant Population

The study will be conducted in healthy male and female volunteers aged 18 to 64 years (inclusive at the time of informed consent) with a subcutaneous fat thickness of at least 3.00 cm (30.0 mm) measured by caliper skinfold method, surrounding the center of localized area of treatment as well as the left and right edges of treatment area at Screening and Day 1.

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 investigational product (IP) (see Section 9.1). 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).

6.5. Summary of Potential Risks and Benefits

Participants may or may not receive direct benefit from participating in this 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.

Clinical data has demonstrated that CBL-514 is well tolerated at doses from 2 to 320 mg, and an ongoing clinical study aims to investigate the safety and tolerability of CBL-514 at doses up to and including the maximal dose. The dose to be used in this study will be confirmed or adjusted after an interim safety report from CBL-0202 has been reviewed by the IRB/IEC, reducing the likelihood of unforeseen risks for study participants.

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) and with the NHMRC National Statement on Ethical Conduct in Human Research 2007 (updated 2018). The conduct of the study will be in accordance with the ICH Integrated Addendum to E6(R1): Guideline for GCP ICH E6(R2).

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 Objective

The primary objective of the study is to evaluate the PK profile of the components of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat.

7.1.2. Secondary Objective

The secondary objectives of the study are to:

- Identify and assess the metabolites of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat.
- Evaluate safety and tolerability of CBL-514 administered into subcutaneous fat.

7.2. Endpoints

7.2.1. Primary Endpoints

The primary endpoints of the study are:

- To evaluate the PK of the components of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat. PK parameters following a single course of administration of CBL-514 will include, but are not limited to the following:
  - Maximum analyte concentration (C_{max})
  - Time to C_{max} (t_{max})
  - Area under the concentration-time curve from time 0 to the last quantifiable concentration (AUC_{0-t})
  - Area under the concentration-time curve from time 0 to 24 hours post-dose (AUC_{024hr})
  - Area under the concentration-time curve from time 0 extrapolated to infinity (AUC_{0-inf})
  - Elimination half-life ($t_{½}$)
  - Apparent total plasma clearance (CL/F)
  - Apparent terminal volume of distribution (V_z/F)

7.2.2. Secondary Endpoints

The secondary endpoints of the study are:

- To identify and characterize the metabolites of CBL-514 in plasma following administration of CBL-514 into subcutaneous fat.

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

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a Phase 2 study to evaluate the safety, tolerability, PK and metabolite profile of CBL-514 injection at the maximal use dosage.

This Phase 2 study has an open-label and single course design. A total of 10 adult participants, composed of 5 females and 5 males, will be enrolled in a single cohort. Each participant will receive a single course of treatment with CBL-514 800 mg on the abdomen (administered as multiple subcutaneous injections) on Day 1 only.

Each participant will participate in the study for approximately 4 weeks, with a maximum expected duration of 61 days including up to 28 days for screening assessments, an Admission/Baseline visit on Day 1 with an overnight stay until Day 2, and 2 Follow-up visits (2 weeks [in-clinic] and 4 weeks [telephone] post treatment).

A schematic of the study design is provided in Figure 1.

Study visits and assessments will occur as delineated in the Schedule of Assessments presented in Table 4.

8.2. Number of Participants

A total of 10 adult participants, composed of 5 females and 5 males, will be enrolled in a single cohort. The sample size is not based on formal hypothesis testing but is consistent with currently accepted standards for exploratory investigation design.

8.3. Dose Adjustment and Safety Oversight

Administration of the IP should be in accordance with dose scheme. Deviations in administration will potentially affect the evaluation of PK.

Safety oversight will be provided by the Investigator, the Sponsor's Representative and the Medical Monitor (MM) as described in the Medical Monitoring Plan and Safety Management Plan.

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

1. Any participant experiences an AE as Grade 3 (as defined in the NCI-CTCAE Version 5.0) for cardiovascular, renal or hepatic events considered to be at least possibly related to IP.
2. 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.

3. Any participant experiences a serious AE (SAE) that is considered to be at least possibly related to the IP.
4. An AE or group of AEs that singularly or in aggregate suggests to the Investigator or Sponsor that the IP is poorly tolerated and further treatment per protocol may not be safe.

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

8.5. Study Termination

The study will be completed as planned unless:

- New information or other evaluation regarding the safety of the study medication indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study. This may be determined by the Sponsor, the Investigator, the IRB/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 early termination (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 IRB/IEC and/or regulatory authority in writing of the study's completion or early discontinuation.

Figure 1: Study Design

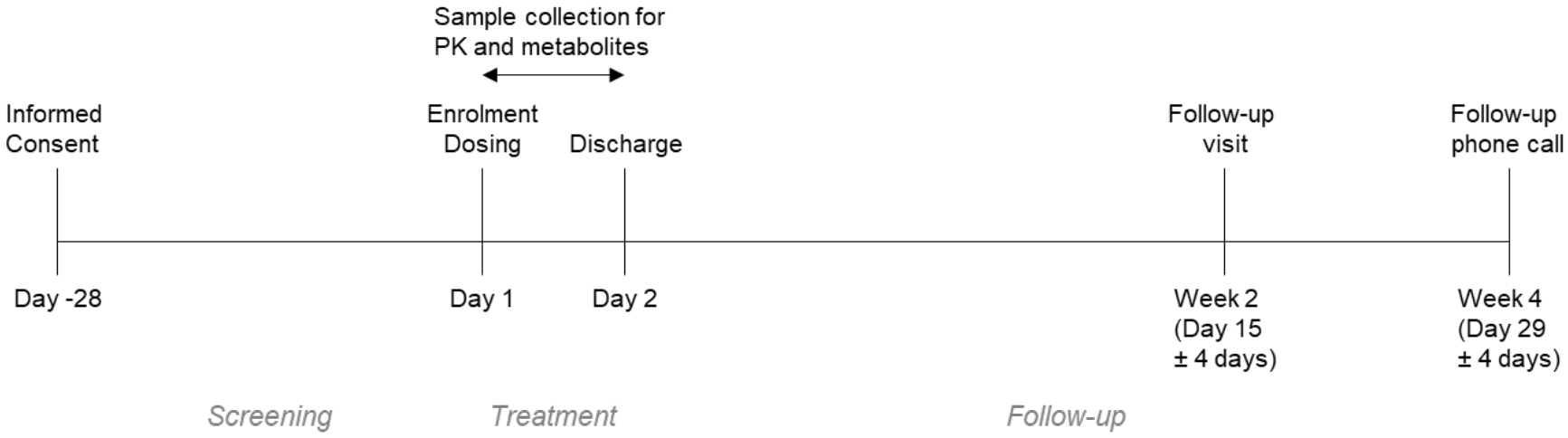

Table 4: Schedule of Assessments

Assessment/Schedule	Screening	Treatment	Follow-up		
			Day 2	Week 2	Week 4
Day	-28 to -1	1*	2	15 ± 4 days	29 ± 4 days
Visit	1	2		3/ET	4/EOS (Telephone)
[redacted]					

Abbreviations: AE = adverse event; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; IP = investigational product; PK = pharmacokinetic.

Notes: *Available measurements of medical evaluations (body weight, abdominal subcutaneous fat thickness, physical examinations, 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.

* [redacted]

9. SELECTION AND WITHDRAWAL OF PARTICIPANTS

9.1. Participant Inclusion Criteria

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

1. Male/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. Participant has sufficient subcutaneous fat thickness of at least 3.00 cm (30.0 mm) measured by caliper skinfold method surrounding the center of localized area of treatment as well as the left and right edges of treatment area at Screening and Day 1.
4. 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, including food and drink restrictions.

9.2. Participant Exclusion Criteria

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

1. Women of childbearing potential (WOCBP) who are not willing to commit to an acceptable contraceptive regimen from the time of Screening and throughout study participation until 90 days after the last IP dose, or who are currently pregnant or lactating. Male participants who are not willing to commit to an acceptable contraceptive method. For details on contraception, refer to Section 9.3.3. Female participants who are not WOCBP are not required to use contraception.

   * Not WOCBP is defined as females who have been surgically sterilized (hysterectomy or bilateral oophorectomy) or who are postmenopausal (defined as at least 50 years, with ≥ 12 months of amenorrhea) with a follicle-stimulating hormone (FSH) > 40 IU/L prior to Screening.
2. Participant diagnosed with coagulation disorders or is receiving anticoagulant/antiplatelet therapy or medications or dietary supplements, which impede coagulation or platelet aggregation.
3. Participant 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. Participant has a clinically significant cardiovascular disease and clinically significant abnormal findings in electrocardiogram (ECG).
5. Participant 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. Participant with a history of human immunodeficiency virus (HIV)-1 infection, or participants with active HIV infection at Screening with positive HIV antigen/antibody (Ag/Ab) combo test.
7. Participants with any hepatic medical condition that, in the opinion of the Investigator, would compromise the participant's ability to undergo study procedures and/or interfere with the assessment of the obtained data.
8. Participants 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.
9. Participant 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. Cicatricial tissue or any abnormality of the skin or soft tissues on the anticipated treatment area,
    c. Grade III cellulite (Nürnberger and Muller scale, Nürnberger 1978) at the area to be treated,
    d. Skin folding on treatment area when the participant is in the supine position,
    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 subcutaneous fat,
    g. Tattoos on the area to be treated.
10. Participant who has 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.
11. Participant is undergoing chronic systemic steroid or immunosuppressive therapy.
12. Requiring continual use of the following therapeutic agents during the study: terfenadine, buspirone, fexofenadine, any medication that is known to strongly inhibit or induce CYP enzymes (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 participant needs to use the above-mentioned therapeutic agents during the study for any reason, these therapeutic agents should not be used for at least 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. Participants with known allergies or sensitivities to the IP or its components.

15. Participants with liver cirrhosis or with inadequate liver function at Screening defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBIL), or gamma-glutamyl transferase (GGT) > 3.0 × upper limit of normal (ULN).
16. Participants with any renal impairment, defined as abnormal serum creatinine, and urea > 1.5 × ULN or estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2. Participants who are currently on dialysis should be excluded.

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

9.3. Prohibitions and Restrictions in the Study

9.3.1. Medication

Concomitant use of the following medications, treatment modalities, or diets are prohibited during the study:

1. Use of anticoagulant/antiplatelet therapy or medications or dietary supplements which impede coagulation or platelet aggregation.
2. Any cosmetic or interventional surgery procedures on area to be treated.
3. Use of terfenadine, buspirone, fexofenadine, 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 participant 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.
4. Use of other investigational drug or device within 4 weeks prior to Screening.

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

9.3.2. Food and Drink Restrictions

During the study the foods and drinks outlined in Table 5 should not be consumed 3 days prior to dosing until all PK samples have been collected.

Table 5: Food and Drink Restrictions During Study Participation

Type of food	Examples
Foods or supplements containing curcuminoids	Curry foods; supplements containing turmeric extracts or curcumin/curcuminoids
Foods or supplements rich in resveratrol	Red wines; red grapes (fruit and/or juice); chocolates; cocoa; peanuts
Alcoholic drinks	Beer; white wines

9.3.3. Contraception

Highly effective contraceptive methods with 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]

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[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 subject 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.

- condom used by male partner during sexual intercourse.

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

9.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Re-screening will be allowed within the recruitment period for the study. Re-screened participants should be assigned a new screening number.

9.5. Participant Replacement

Participants who are enrolled but who do not receive any IP will be replaced and the replacement participant will be assigned the same treatment as the participant they are replacing.

Participants who discontinue the study at any time after the initiation of dosing will be retained in the Safety Population, however additional participants may be recruited at the discretion of the Sponsor to obtain an evaluable PK Population and/or Metabolite Population.

9.6. Participant Withdrawal Criteria

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

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

- Participant voluntarily withdraws consent,
- Participant cannot meet the dosing compliance specified the Section 10.5,
- Any other clinical AE, medical condition, or situation arises, that in the opinion of the Investigator it would not be in the best interest of the participant to continue participation.

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

If a participant is withdrawn due to a lack of dosing compliance, a clear reason for not completing the treatment must be recorded. The collection of PK samples post-dose will not be

performed. Before discharge, safety assessments post-dose on Day 1 will be completed and an Early Termination visit will be planned.

If a participant asks or decides to withdraw from the study, all efforts will be made to complete and report the observations, especially those related to the listed primary and secondary objectives, as thoroughly as possible up to the date of withdrawal. A clear and concise reason for withdrawal will be identified and recorded on the appropriate eCRF, along with the date of withdrawal.

10. TREATMENTS

10.1. Treatments Administered

10.1.1. Investigational Product

CBL-514 is a lipolysis injection product developed by Caliway Biopharmaceuticals Co., Ltd. CBL-514 is constituted by curcumin and *trans*-resveratrol.

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

CBL-514 should be stored at 4°C, with an allowed temperature range of between 2°C and 8°C.

Table 6: CBL-514 Product Details

Name	CBL-514
Active Ingredients	Curcumin and *trans*-resveratrol
Dosage form	Subcutaneous Injection, [redacted] of CBL-514, 20 mL/vial
Pharmacological category	D11AX other dermatological

10.1.2. Reference Products

Not applicable.

10.2. Dosage and Treatment Periods

All 10 participants enrolled in the study will receive a single course of treatment with CBL-514 800 mg on the abdomen (administered as multiple subcutaneous injections) on Day 1 only. The IP administration should be completed within 60 minutes.

In order to reach the maximal CBL-514 dose of 800 mg while limiting the number of injections, [redacted].

The dosing scheme is presented in Table 7.

Table 7: Dosing Scheme

Treatment Area	Dose level (mg/cm^2)	Injection volume per 7.5 cm^2 grid (mL)	Administration			
			No. of injections	Total injection volume (mL)	Total CBL-514 (mg)	
Abdomen	2.0	[redacted]	[redacted]	160	800	Curcumin [redacted] Resveratrol [redacted]

10.3. Method of Assigning Participants to Treatment

The study has an open-label and single course design. All 10 participants will receive CBL-514 at the same dose (Table 7).

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

10.4. Concomitant Medications

All medications*, including OTC medications, and dietary supplements, taken during the 6 months prior to the Screening visit will be recorded and reviewed by the Investigator to determine whether the participant 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 participants 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. Prior and concomitant medications will be listed by participant and summarized by anatomical therapeutic chemical (ATC) and Preferred Term (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.

10.5. Treatment Compliance

The IP, CBL-514, will be administered at the study site by the designated study staff under guidance of Investigator or designee.

If a participant’s IP 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 IP administration and accompanying activity will be recorded in the eCRF. The number of syringes administered will be documented in the participant’s source documents.

A dosing compliance less than 90% or more than 110% of total dosage per treatment is a major deviation and may be deemed to have an influence on PK. Effort should be made to adhere to the study design. Compliance is defined as the dosage administered out of the total dose or number of injections out of the amount required per treatment in accordance with protocol.

10.6. Blinding

Not applicable.

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 was manufactured under GMP and is suitable for human use.

11.2. Study Drug Packaging and Labeling

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

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

11.3. Study Drug Storage

Upon receipt, the IP must be stored at 4°C, with an allowed temperature range of between 2°C and 8°C. Appropriate storage conditions must be ensured by completing a temperature log in accordance with local requirements on a regular basis (e.g., by temperature logging devices that record every 30 minutes), showing minimum and maximum temperatures reached over the time interval. Refer to Pharmacy Manual for further details.

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 participants, the vials should be warmed up to room temperature. The solution of CBL-514 should be used before the expiry date.

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

11.5. Administration

A single course of CBL-514 will be administered as multiple subcutaneous injections on the abdomen. Oral analgesia as per standard of care will be administered to participants approximately 1 hour prior to IP administration. Topical anesthesia cream will be applied to the treatment area, followed by local anesthesia injection, both as per standard of care. If needed, participants may undergo ice compress immediately prior to IP injection. The IP administration should be completed within 60 minutes.

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. At the end of the study, the IP 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 remaining at the investigational site will be returned to the Sponsor or its designee in accordance with the Sponsor's instruction. If the destruction of IP is allowed at the 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 is provided in Table 4.

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

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

Prior to enrolling in the study, and before performance of any procedures, potential participants 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, participants 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:

[1] ECG to be performed in supine position after at least 5 minutes rest, prior to vital sign assessments.

- [redacted]

12.2. Visit 2: Baseline and Treatment (Day 1 to Day 2)

Visit 2 will involve an overnight stay at the study site (Day 1 to Day 2).

12.2.1. Day 1: Before Dosing

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

- [redacted]

[1] Available measurements of medical evaluations (body weight, abdominal fat thickness, physical examinations, 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.
[2] If IP dose is within 7 days of Screening pregnancy test, pregnancy test on Day 1 will not be necessary to assess.
[3] Blood samples for PK analysis will be collected from all 10 subjects. Of these 10 subjects, 6 subjects (the first 3 females and the first 3 males enrolled) will have additional blood samples collected for metabolite assessment.

[redacted]

12.2.2. Day 1: Dosing

CBL-514 will be administered by assigned clinical staff. The IP administration should be completed within 60 minutes.

12.2.3. Day 1 and Day 2: After Dosing

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

The following procedures will be conducted:

[redacted]

[1] Blood samples for PK analysis will be collected from all 10 subjects. Of these 10 subjects, 6 subjects (the first 3 females and the first 3 males enrolled) will have additional blood samples collected for metabolite assessment.

A participant who is withdrawn from the study due to a lack of dosing compliance will not continue with the collection of PK samples post-dose. Before discharge, physical examination, vital signs, and AE assessment will be performed, and a participant diary will be dispensed.

12.3. Visit 3: Follow-up (Week 2) or Early Termination (ET)

Participants will return to the study site during the follow-up period on Day 15 (± 4 days).

The following assessments will be conducted at Visit 3:

12.4. Visit 4: Telephone Follow-up (Week 4) and End of Study (EOS)

Participants will be contacted by telephone during the follow-up period on Day 29 (± 4 days).

The following assessments will be conducted at Visit 4:

This visit marks the end of participation in this study.

[1] At Week 4, only information for medication related to AEs will be collected.

13. PHARMACOKINETIC ASSESSMENTS

13.1. Blood Sample Collection

Blood samples for PK and metabolite analysis will be obtained, according to the site's standard operating procedures at the following time points on Day 1 and Day 2: pre-dose (within 30 minutes prior to scheduled dosing), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), 5 hours (± 10 minutes), 6 hours (± 10 minutes), 7 hours (± 10 minutes), 8 hours (± 10 minutes), 10 hours (± 10 minutes), 12 hours (± 10 minutes), 18 hours (± 10 minutes), and 24 hours (± 10 minutes) post-dose (from the start of CBL-514 administration).

The actual collection time of each sample must be recorded in the source data documentation, on the collection tube and in the eCRF. The allowed time deviation window for post-dose blood sample collection is 10 minutes before a deviation is recorded.

PK samples will be collected from all 10 participants. Of these 10 participants, 6 participants (the first 3 females and the first 3 males enrolled) will have additional samples collected for metabolite assessment.

13.2. Sample Analysis

Plasma PK and metabolite sample analysis will be performed using validated procedures and methods.

The Sponsor will supply complete written instructions for handling, processing, storage, and shipping of samples prior to study initiation.

14. SAFETY ASSESSMENTS

14.1. Safety Parameters

Study procedures should be completed as delineated in the Schedule of Assessments (Table 4). However, if a participant is unable to attend a visit within the specified window, the Investigator or designee should discuss appropriate scheduling with the Sponsor's MM or appropriate designee. Any unscheduled procedures required for urgent evaluation of safety concerns must take precedence over all routine scheduled procedures.

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 schedule with participants resting for at least 5 minutes in a supine position. Vital sign assessments include temperature, pulse rate, blood pressure, and respiratory rate. The same method for collection temperature should be used consistently. 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 which include body height (centimeters), body weight (kilograms), and abdominal subcutaneous fat thickness (millimeter) will be measured at the time points delineated in the study schedule.

Body height and body weight will be used to calculate BMI. BMI is calculated by dividing the participant's body weight in kilograms by the participant's height in meters squared (kg/m^2). Body weight and height will be obtained with the participant's shoes and jacket or coat removed.

Abdominal subcutaneous fat thickness will be measured by caliper skinfold test. The position of skinfold test by caliper will be performed surrounding the center of treatment area as well as the left and right edges of treatment area.

14.1.4. Injection Site Reactions

Participant diaries will be provided to the participants, and the participants will be asked to record if there are any changes to the injection site(s) or any discomforts in between visits. The diary will be reviewed and used to identify AEs by the Investigator, or delegate, at Week 2 visit or other follow-up visits, as needed. ISRs will be recorded as AEs and severity will be assessed according to the CTCAE, Version 5.0; please refer to Table 8.

All 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 schedule (Table 4).

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

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

14.1.6. Electrocardiogram

A 12-lead ECG (including parameters: heart rate, RR interval, PR interval, QT interval, QTcF interval, and QRS interval, as well as overall interpretation) will be taken at the time points delineated in the study schedule (Table 4). Additional ECG monitoring may be performed at other times if deemed necessary.

ECGs will be performed prior to vital signs with participants in a supine position. Participants 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.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring the blood draw is within the window specified in the protocol.

14.1.7. Laboratory Assessments

Safety laboratory tests (hematology, biochemistry, coagulation, and urinalysis) will be performed at the time points specified in the study schedule (Table 4). Additional clinical laboratory tests may be performed at other times if deemed necessary based on the participant'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 (MCV)
- Mean corpuscular hemoglobin (MCHC)

14.1.7.2. Biochemistry

Biochemistry parameters to be tested are:

- Urea (U)
- Creatinine (CREAT)
- Total Bilirubin (TBIL)
- Albumin (ALB)
- Alkaline Phosphatase (ALP)
- Aspartate Aminotransferase (AST)
- Alanine Aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)
- Estimated Glomerular Filtration Rate (eGFR)
- Glycated hemoglobin (HbA1c) (at Screening only)
- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Bicarbonate (BICARB)
- Triglyceride
- Total cholesterol
- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (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 participant at Screening and other times according to the study schedule. If any clinically significant abnormality is noted for protein, blood, nitrite or leukocyte esterase (and at the discretion of the Investigator) a microscopic analysis of urine, examining for RBC, WBC, bacteria and casts, will be performed.

Macroscopic urinalysis parameters to be tested are:

- pH (PH)

- Specific Gravity (SPGRAV)
- Protein (PROT)
- Glucose (GLUC)
- Ketones (KETONES)
- Bilirubin (BILI)
- Blood (BLD)
- Nitrite (NITRITE)
- Urobilinogen (UROBIL)
- Leukocytes (WBC)

14.1.7.5. Viral Serology

HIV Ag/Ab combo test, Hepatitis B surface antigen (HBsAg), Hepatitis B virus (HBV) surface and core antibody test, and Hepatitis C virus (HCV) antibody testing will be performed at Screening.

14.1.7.6. Pregnancy Testing

All WOCBP will be tested for pregnancy by a serum beta human chorionic gonadotropin (β-hCG) test pregnancy test at Screening. Urine β-hCG strip pregnancy testing will be performed for all other scheduled visits. Additional tests will be performed if a participant 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 postmenopausal (defined as at least 50 years with cessation of regular menstrual periods for at least 12 months) or must have been surgically sterilized (hysterectomy or bilateral oophorectomy). Postmenopausal status will be confirmed through testing of FSH levels at Screening.

14.2. Adverse and Serious Adverse Events

In this study, AEs will be reported for all participants from the time of consent until the completion of the End of Study (EOS) phone call/ET visit. SAEs will be reported for all participants (enrolled and not enrolled) from the time of consent. AEs reported from the time of consent to pre-dose on Day 1 will be recorded as pre-treatment AEs. TEAEs will be evaluated from the first administration of the IP until the EOS phone call/ET visit. AEs that are deemed related to treatment and are ongoing 14 days post EOS/ET for non-serious AEs and 60 days post EOS/ET for SAEs, the 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 participant'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
- 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 to Table 8.

Table 8: 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 ADL*.
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. 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.

Abbreviations: ADL = Activities of daily living.
Notes: A semi-colon indicates 'or' within the description of the grade.
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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 9.

Table 9: 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.

Abbreviations: IB = Investigator's Brochure; IP = investigational product; PK = pharmacokinetics.

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

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

AESIs in this study include the following events:

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.

AESIs are to be reported to the Sponsor 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, 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-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above

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

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

Notes:

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

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

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

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

14.2.6. Recording Adverse Events

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

However, abnormal values that constitute an SAE or lead to discontinuation of administration of the 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 participant to discontinue the study. AEs that occur during the study must be documented in the participant's medical record, on the AE eCRF and on the SAE report form. If an SAE report is completed, pertinent laboratory data should be recorded on the SAE form, preferably with Baseline values and copies of laboratory reports.

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

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 14.2.3. An AE of severe intensity may not be considered serious.

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

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

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

14.3. Followup of Adverse Events and Serious Adverse Events

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

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

14.4. Pregnancy

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

All WOCBP will be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during the trial. Male participants 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 participant becomes pregnant during the clinical trial, the Investigator will report the details on a Pregnancy Form to the Sponsor/assigned designee within 24 hours of knowledge of the pregnancy. Even though participants agree to withdraw or terminate the clinical trial, the Investigator should follow-up and document the process and results of all the pregnancies.

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

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

The Sponsor 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 participant confidentiality is respected.

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

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

16. STATISTICS

Statistical methods will be further outlined in a statistical analysis plan (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. The SAP will be finalized prior to locking 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 data will be handled and processed according to the Sponsor's representative standard operating procedures, which are written based on the principles of GCP. 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.

In general, descriptive statistics (e.g., arithmetic mean, SD, median, minimum and maximum) will be calculated for continuous safety and PK data by treatment and protocol specified time point, while frequency summary (e.g., number of observed and percentage of each categories) will be applied for categorical safety data by treatment and protocol specified time point. No adjustments will be made for missing or incomplete data.

The Baseline value is defined as the last available result collected/derived prior to IP administration. The change from Baseline value is defined as the difference between the result at the post Baseline time point and the Baseline value.

All collected and derived data will be listed.

16.1. Sample Size

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

16.2. Analysis Populations

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

16.2.1. Pharmacokinetic (PK) Population

The PK Population will consist of all participants who receive any amount of IP and have sufficiently evaluable concentration-time profiles of plasma curcumin and/or resveratrol to allow determination of at least one PK parameter among C_{max}, t_{max}, and $AUC_{0\text{-}24hr}$. An evaluable PK profile will be determined at the discretion of the pharmacokineticist following examination of participants with dosing or protocol deviations that could potentially affect the PK profile. The PK Population determination will be done by the study pharmacokineticist post database lock.

16.2.2. Metabolites Population

The Metabolites Population will consist of all participants who receive any amount of IP and have at least one quantifiable concentration of any identified metabolite(s) of curcumin and/or resveratrol.

The Metabolite Population will be used for presenting individual and summary concentrations only without PK analysis and/or PK parameters. Any participant or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

16.2.3. Safety Population

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

16.3. Statistical Methods

16.3.1. Participant Disposition

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

16.3.2. Demographics, Medical History, and Baseline Characteristics

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

Medical history terms will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the start of the study. Medical history will be analyzed using descriptive statistics by MedDRA® System Organ Class (SOC) and PT for the Safety Population.

16.3.3. Prior and Concomitant Medication

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

16.3.4. Treatment Compliance and Exposure

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

16.4. Safety Analyses

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

16.4.1. Adverse Events

AEs will be coded using the most current version of the MedDRA® available at the start of the study. A by-participant AE data listing, including verbatim term, PT, SOC, severity and relationship to IP, will be provided. The number of participants experiencing TEAEs and number

of individual TEAEs will be summarized by SOC and PT. TEAEs will also be summarized by severity and by relationship to IP. SAEs will also be summarized.

16.4.2. Laboratory Evaluations

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

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

16.4.3. Vital Signs

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

16.4.4. Electrocardiograms

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

16.4.5. Other Safety Assessments

The following assessments will be listed by participant:

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

16.5. Pharmacokinetics

Plasma concentrations for curcumin and resveratrol, and actual blood sampling times will be listed by protocol specified time point and summarized using descriptive statistics – number of measurements, arithmetic mean, SD, and %CV, geometric mean, minimum, median, and maximum – at each scheduled time point. Individual and mean plasma concentration time profiles will also be presented graphically.

PK parameters for plasma curcumin and resveratrol will be determined from the individual plasma concentrations by a non-compartmental method using Phoenix WinNonlin® software.

The following PK parameters will be estimated (Table 10):

Table 10: Pharmacokinetic Parameters to be Estimated

Parameter	Definition
C_{max}	Maximum analyte concentration, which is directly determined from the plasma concentration-time profiles.
T_{max}	Time to maximum analyte concentration. If the same C_{max} concentration occurs at different time points, t_{max} is assigned to the first occurrence of C_{max}.
AUC_{0-t}	Area under the concentration-time curve from time 0 (time of dosing) to the last quantifiable concentration, using the 'Linear Up and Log Down' method.
AUC_{0-24hr}	Area under the concentration-time curve from time 0 (time of dosing) to 24 hours post-dose, using the 'Linear Up and Log Down' method.
AUC_{0-inf}	Area under the concentration-time curve from time 0 (time of dosing) extrapolated to infinity, using the following formula using the following formula: $AUC_{0-inf} = AUC_{0-t} + Ct/k_{el}$
$AUC_{\%extrap}$	The percentage of the AUC that has been extrapolated beyond the last observed/quantified data point, using the following formula: $AUC_{\%extrap} = (AUC_{0-inf} - AUC_{0-t}/AUC_{0-inf})*100$
k_{el}	The apparent terminal elimination rate constant, which will be estimated from a regression of ln(C) versus time over the terminal log-linear drug disposition portion of the concentration-time profiles.
$t_{½}$	Apparent terminal half-life, using the following formula: $t_{½} = ln(2)/k_{el}$
CL/F	Apparent total plasma clearance, using the following formula: $CL/F = Dose/AUC_{0-inf}$
Vz/F	Apparent terminal volume of distribution, using the following formula: $Vz/F = Dose/(k_{el}.AUC_{0-inf})$

Value for $t_{½}$, k_{el}, AUC_{0-inf}, CL/F or Vz/F will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile. Additional analyses will be performed as deemed necessary upon review of the data.

Any identified metabolite(s) concentrations of curcumin and/or resveratrol will only be presented for listings and summary without PK analysis and/or PK parameters.

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

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

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

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

17.4. Data Protection

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

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

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all study-related (essential) documentation. These include, but are not limited to, IRB/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 participants 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. Participant confidentiality will be maintained by referring to individual participants by their identifying code used in the trial. Data will not be released publicly until the manuscript is accepted for publication. In the case of no publication, information will only be released to the public and media in accordance with the Sponsor's approval.

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

The results summary will be posted to the 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 participants who wish to participate in the study.

The Investigator must ensure that the participant's anonymity is also maintained. Participants should only be identified by their initials and a participant 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 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 participants
- 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 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 participants. 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

Adatto MA, Adatto-Neilson RM, Morren G. Reduction in adipose tissue volume using a new high-power radiofrequency technology combined with infrared light and mechanical manipulation for body contouring. Lasers Med Sci. 2014 Sep;29(5):1627-31.

American Society of Aesthetic Plastic Surgery. Cosmetic Surgery National Data Bank Statistics c2020 – [cited 2021 June 29]. Available from: https://cdn.surgery.org/media/statistics/aestheticplasticsurgerynationaldatabank-2020stats.pdf

Atiyeh BS, Ibrahim AE, Dibo SA. Cosmetic mesotherapy: between scientific evidence, science fiction, and lucrative business. Aesthetic Plast Surg. 2008 Nov;32(6):842-9.

Duncan D, Rotunda AM. Injectable therapies for localized fat loss: state of the art. Clin Plast Surg. 2011 Jul;38(3):489-501, vii.

Friedmann DP. A review of the aesthetic treatment of abdominal subcutaneous adipose tissue: background, implications, and therapeutic options. Dermatol Surg. 2015 Jan;41(1):18-34.

Grazer FM, de Jong RH. Fatal outcomes from liposuction: census survey of cosmetic surgeons. Plast Reconstr Surg. 2000 Jan;105(1):436-46; discussion 447-8.

Jalian HR, Avram MM. Body contouring: the skinny on noninvasive fat removal. Semin Cutan Med Surg. 2012 Jun;31(2):121-5.

Kennedy J, Verne S, Griffith R, Falto-Aizpurua L, Nouri K. Non-invasive subcutaneous fat reduction: a review. J Eur Acad Dermatol Venereol. 2015 Sep;29(9):1679-88.

Nestor MS, Newburger J, Zarraga MB. Body contouring using 635-nm low level laser therapy. Semin Cutan Med Surg. 2013 Mar;32(1):35-40.

Nürnberger F, Müller G. So-called cellulite: an invented disease. J Dermatol Surg Oncol. 1978 Mar;4(3):221-9.

Rotunda AM, Kolodney MS. Mesotherapy and phosphatidylcholine injections: historical clarification and review. Dermatol Surg. 2006 Apr;32(4):465-80.

24. APPENDIX

24.1.