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STATISTICAL ANALYSIS PLAN

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

PROTOCOL NO.: CBL-0202

PRODUCT CODE: CBL-514

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Document History Changes made from SAP V1.0 in Addendum 1.0

1.	**Changes in SAP text:** The following changes are made from final approved SAP: Reference to Imputation methods and outputs from Section 10 are removed: Efficacy and other sections of SAP wherever imputation method is given. **Justification of change from final SAP:** It was not realized until later that the definition of missing data between Caliway and [redacted] is different. Per study design, there are visits can be skipped or no need to be completed. From Caliway's perspective, only visit that should be completed per protocol but not completed can be deemed as missing. But from [redacted] perspective, all visits not completed will be deemed as missing regardless of the missing reason. Therefore, Caliway decided to remove imputation from the SAP at this time point as it does not work the way Caliway originally thought it will be.
2.	**Changes in Mock shell**: TFLs with imputations are removed.

SAP APPROVAL

By my signature, I confirm that changes from SAP V1.0 in Addendum 1.0 has been reviewed by Caliway Biopharmaceuticals Australia Pty Ltd and has been approved for use on the CBL-0202 study:

Name	Title / Company	Signature	Date
[redacted]	Senior Clinical Project Specialist/ Caliway Biopharmaceuticals Australia Pty Ltd		

By my signature, I confirm that changes from SAP V1.0 in Addendum 1.0 has been reviewed by [redacted] and has been approved for use on the CBL-0202 study:

Name	Title / Company	Signature	Date
Prepared by: [redacted]	Senior Biostatistician / [redacted]		
Reviewed by: [redacted]	Senior Biostatistician/ [redacted]		

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List of Abbreviations

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
APTT	Activated Partial Thromboplastin Time
ATC	Anatomical Therapeutic Class
CI	Confidence Interval
CS	Clinically Significant
CSR	Clinical Study Report
DBP	Diastolic blood pressure
ECG	12-Lead Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ET	Early Termination
FBS	Fasting Blood Sugar
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
IP	Investigational Product
ISR	Injection Site Reaction
ITT	Intent-to-Treat
LDL-C	Low-Density Lipoprotein Cholesterol
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
NCS	Not Clinically Significant
NK	Not Known
PI	Principal Investigator
PT	Preferred Term
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
S.I.	International System of Units
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The following Statistical Analysis Plan (SAP) provides the outline for the statistical analysis of the data collected from the CBL-0202 study (protocol version 8.0 dated 1 March 2023).

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design

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

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

will be enrolled across the 2 stages of the study.

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

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

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

Based upon SRC recommendation intermediate doses may be explored.

The dosing scheme is presented in Table 1.

Table 1: Dosing Scheme-Stage 1

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

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

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

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

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

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

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

During Stage 1 of the study, the SRC will meet after all subjects in a dose group have completed the Week 1 visit. The SRC will review all reported AEs, AESIs, laboratory trends, and vital signs of all subjects from each dose group. Based upon review of available safety and tolerability data from each preceding dose group, the SRC will make a decision on progressing to the next dose group.

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

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

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

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

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

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

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

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

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

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

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

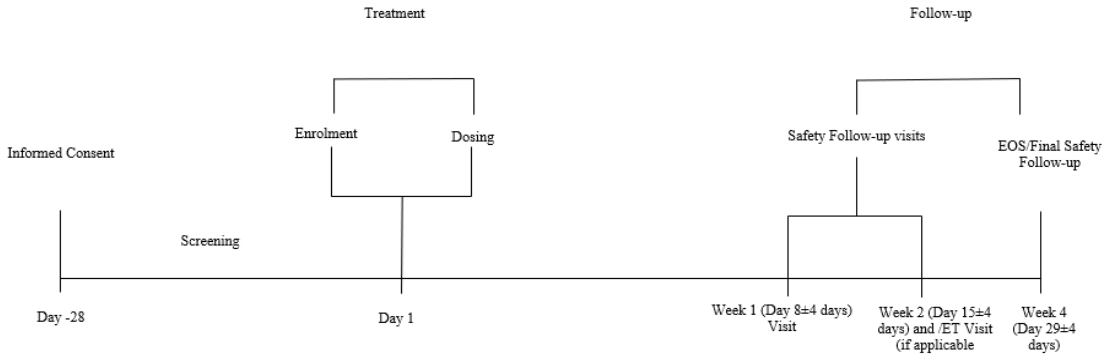
A subject diary will be provided to each subject to record if there are any changes to the injection site/s or any discomforts in between visits. Subjects will be instructed to bring the subject diary with them for all visits to the clinic.

Table 2: Maximum Dosing Scheme-Stage 2

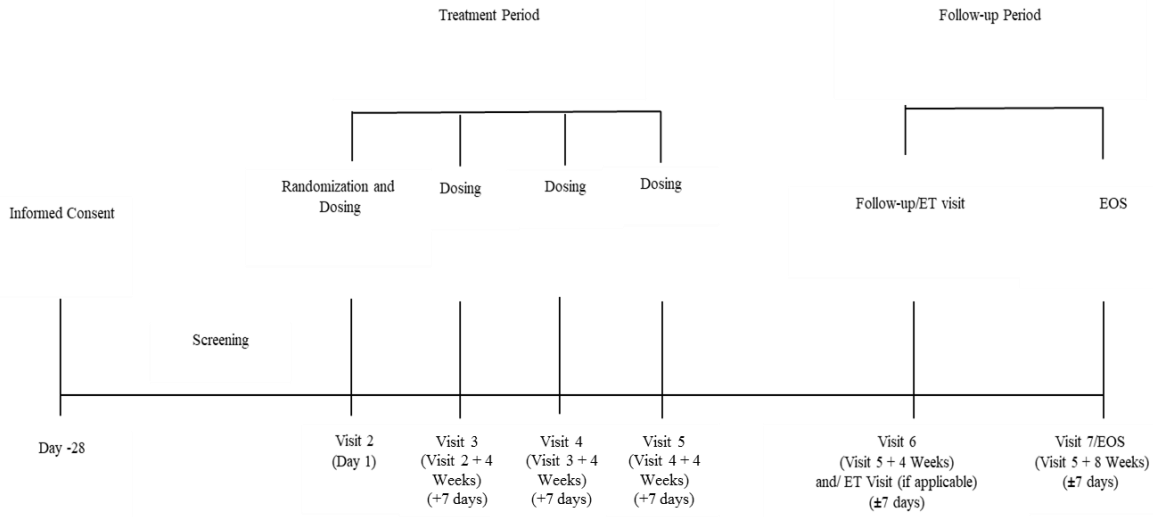
Group	**CBL-514 Dose Level (mg/cm^2)**	**Injection volume per injection in 6.0 cm^2 grid space**	**Administration for one dose**			
			No. of Injection	**Total Injection Volume of IP (mL)**	**Total CBL-514 (mg)**	
CBL-514	2.0	2.4 mL	50	120	600	[redacted]
Placebo	-	2.4 mL	50	120	-	-

Figure 1: Study Design

Stage 1



Stage 2



2.2 Objectives

2.2.1 Primary objectives

Stage 1:

The primary objective of Stage 1 the study is to:

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

Stage 2:

The primary objective of Stage 2 of the study is to:

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

2.2.2 Secondary objectives

Stage 1:

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

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

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

Stage 2:

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

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

2.3 Endpoints

2.3.1 Primary endpoints

Stage 1:

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

Stage 2:

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

2.3.2 Secondary endpoints(s)

Stage 1:

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

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

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

Stage 2:

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

2.4 Sample Size

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

2.5 Randomization

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

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

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative [redacted] Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP).

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings and will be listed and sorted by treatment arm participant number and visit, where applicable. All descriptive summaries will be presented by treatment group and nominal visit/time point (where applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD and median values will be displayed to one more decimal than the source data for the specific variable.

  95% Confidence Intervals (CIs), mean differences (among treatments and from baseline) and least-square (LS-Means) values will be displayed to one more decimal than the source data for a specific variable. P-values will be displayed to 5 decimal places.

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the above mentioned rules.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of participants in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place. Proportions will be displayed to 3 decimal places.

  95% Confidence Intervals (CIs), difference in proportions, and other categorical parameters will be displayed to one decimal place for percentages. Proportions will be displayed to 3 decimal places. P-values will be displayed to 5 decimal places.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows.

- Result display convention: Results will be center aligned in all summary tables and listings. Participant identifiers visit and parameter labels may be left-aligned if required.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  Date only: YYYY-MM-DD

  Date and time: YYYY-MM-DD HH:MM

If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2016-NK-NK'. Times will be reported in military time.

3.2 Key Definitions

The following definitions will be used:

- Subcutaneous Fat Thickness: Subcutaneous fat thickness can be calculated by the mean of ultrasound results of subcutaneous fat thickness at 4 ultrasound scan spots on abdomen including far left, left, far right, and right spots:

  Subcutaneous Fat Thickness = [Ultrasound Result (Far Left) + Ultrasound Result (Left) + Ultrasound Result (Right) + Ultrasound Result (Far Right)] / 4

- Subcutaneous Fat Volume:
  - Stage 1: Subcutaneous fat volume over treated area for each treatment group in Stage 1 will be calculated using the following formulas as suggested in the previous Caliway studies:

CBL-514 480 mg: Subcutaneous Fat Volume(mL) = Subcutaneous Fat Thickness(cm) × 240 cm^2

CBL-514 640 mg: Subcutaneous Fat Volume(mL) = Subcutaneous Fat Thickness(cm) × 320 cm^2

CBL-514 800 mg: Subcutaneous Fat Volume(mL) = Subcutaneous Fat Thickness(cm) × 400 cm^2

  - Stage 2: Assuming the treatment area is 300 cm^2 (which is the area for the maximum dose of 50 injections) subcutaneous fat volume over treated area will be calculated using the following formula as suggested in the previous Caliway studies:

Subcutaneous Fat Volume(mL) = Subcutaneous Fat Thickness(cm) × 300 cm^2

- Baseline: The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each participant prior to first study drug administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

Change from Baseline Value = Result at Visit/Time Point – Baseline Value

- The change of subcutaneous fat thickness and fat volume from baseline value at a post-baseline visit/time point will be calculated using the following formulas:

Change of Subcutaneous Fat Thickness from Baseline Value = Subcutaneous fat thickness value at Visit/Time Point – Subcutaneous fat thickness value at Baseline

Change of Subcutaneous Fat Volume from Baseline Value = Subcutaneous Fat Volume value at Visit/Time Point – Subcutaneous fat volume value at Baseline

  The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

- Percent Change from Baseline: The percent change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value and then divide by the baseline value which will be multiplied by 100 to display as a percentage.

The percent change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula:

$$\text{Percent Change from Baseline Value} = \frac{\text{Result at Visit} - \text{Baseline Value}}{\text{Baseline Value}} \times 100$$

The percent change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

- Study day: The study day of an event is defined as the relative day of the event starting with the date of the first study drug administration (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the first study drug administration will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of First Study Drug Administration) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

  Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.

- Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.
- Concomitant Medications: Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of the study drug. Medications that were stopped on the same date as the first study drug administration will be defined as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant
- Treatment Emergent Adverse Events (TEAEs): TEAEs are defined as adverse events that occurred following the first administration of study medication.
- Treatment related TEAEs: Treatment related TEAEs include the TEAEs which are deemed definitely, probably, or possibly related to study drug.
- Conversion of categorical values: In some instances, continuous variables are expressed as a range (i.e. < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs.

3.3 Multiple Comparisons and Multiplicity Adjustments.

All analyses will be performed without adjustment for multiple endpoints.

3.4 Handling of Missing Data

For the classification of Treatment emergent adverse event (TEAE) and Concomitant medication, the following will be applied in the following order:

a. If all dates/times (start and stop) missing, the event/medication will automatically be classified as a TEAE/Concomitant medication.

b. For AEs with a missing start date/time, if the event end date/time is prior to first study drug administration, the event will not be classified as a TEAE.

c. If only the AE start year/ medication end year is present and is the same or is after the first study drug administration year unit, the event/medication will be classified as a TEAE/Concomitant medication.

d. If the AE start month and year/medication end month and year are present and are the same or after the first study drug administration month and year units, the event/medication will be classified as a TEAE/Concomitant medication.

3.5 Coding of Events and Medications

Medical history and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using the latest version available at the time of study commencement. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary using the latest version available at the time of study commencement. Medications will be mapped to the full WHO-DD Anatomical Therapeutic Chemical (ATC Level 4) class hierarchy, but PTs will be of primary interest in this analysis.

3.6 Treatment Groups

Descriptive analyses will display the following treatment groups:

Stage 1:
- CBL-514 320 mg
- CBL-514 480 mg
- CBL-514 640 mg
- CBL-514 800 mg
- Stage 1 Overall

Stage 2:
- CBL-514 600 mg
- Placebo
- Stage 2 Overall

Descriptive summary analysis of continuous and categorical variables will be conducted as described in section 3.1.

4. ANALYSIS POPULATIONS

In this study 3 analysis populations are defined: The Intent-to-Treat (ITT), Safety population and Per Protocol (PP).

Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final CSR as exploratory post hoc analyses, including analyses for additional study populations or subgroups of interest.

4.1 Population Descriptions

4.1.1 Intent-to-treat (ITT Population)

All assigned or randomized subjects, regardless of whether they receive treatment or not, will be included in the ITT population. Summaries, listings, and analyses by treatment group will be based on the subject's randomly assigned treatment, not what they actually received.

All demographic data analysis will be based on the ITT population. All listings will be presented by the ITT population.

4.1.2 Full Analysis Set Population (FAS Population)

The full analysis set (FAS) population will be defined as all randomized subjects who receive at least one course of IP and contribute qualified baseline and at least one post-dose efficacy assessment measured by ultrasound.

4.1.3 Safety Population

The Safety population will be defined as all randomized participants who received at least one dose of study drug and will be based on actual treatment received. Screen failures and randomized subjects who did not receive any medication will be excluded from the safety analysis set.

All safety analyses will be based on the Safety population.

4.1.4 Per Protocol (PP) population

<u>Stage 1:</u>

1. A subset of FAS population
2. Subjects without any efficacy related major protocol violations
3. Subjects who complete the proposed dosing schedule of study drug (i.e. did the participant complete the study= Yes) and complete all follow-up visits after treatment
4. Subjects whose body weight remain stable throughout the study, identified as having body weight change < 3% based on Day 1 body weight. When the body weight data is missing, the subject will be regarded as having a stable body weight.

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

<u>Stage 2:</u>

1. A subset of FAS population
2. Subjects without any efficacy related major protocol violations
3. Subjects who complete all proposed dosing schedules of study drug (i.e., did the participant complete the study= Yes) and complete 2 follow-up visits after treatment (including the subject who has dose adjustment judged by the Investigator)
4. Subjects have all visits of IP administration within 6 weeks

5. Subjects whose body weight remain stable throughout the study, identified as having body weight change < 2.5 kg compared to last visit and change of body weight < 3 kg compared to Day 1 body weight
6. Subjects whose Visit 6 is performed 3 to 5 weeks post final treatment
7. Subjects whose Visit 7 is performed 7 to 9 weeks post final treatment

However, a subject who was discontinued due to an AE, or died before the required exposure could be met, will still be included in this population. (Such subject should continue to satisfy the PP population criteria outlined in items 1, 2 and 5 above; Furthermore, if scheduled visits attended by the subject. That must adhere to the specified time frames outlined in items 4, 6 and 7 above.)

5. PARTICIPANT DISPOSITION AND ANALYSIS POPULATIONS

Participant disposition and analysis population analysis will be based on all subjects. Participant disposition and analysis populations will be summarized descriptively as described in section 3.1 (categorical descriptive analysis).

5.1.1 Participant Disposition

Participant disposition will include the number of subjects screened, enrolled, screen fails, participants who completed the study as planned and participants withdrawn from the study, as well as the primary reason for early termination. Participant disposition will be summarized descriptively.

5.1.2 Analysis Populations

The number of participants included in each study populations will be summarized descriptively.

In addition, the inclusion of each participant into/from each of the defined analysis populations will be presented in the by-participant data listings.

6. PROTOCOL DEVIATIONS

Protocol deviations will be presented for each participant in the by-participant data listings.

Prior to database lock, all protocol deviations will be reviewed by medical monitors and assigned a status of Important if qualifying as such. i.e., efficacy related major protocol violations.

Protocol deviations and important protocol deviations will be categorized as noted in the Protocol Deviation Management Plan version 2.0 dated 13May202.

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline information will be summarized descriptively as described in section 3.1.

7.1 Demographics

Demographic variables will be summarized using descriptive statistics in accordance with section 3.1 based on the ITT population. The following demographic parameters will be analyzed:

Continuous descriptive analysis:

- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Categorical descriptive analysis:

- Sex
- Race
- Ethnicity

Demographics variables will also be listed by stage and treatment group (section 3.7) under ITT population sorted by subject ID.

7.2 Medical /Surgical history

Medical / Surgical history will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®). Subjects with any past or ongoing medical history will be summarized by system organ classification (SOC) and preferred term (PT) using descriptive statistics in accordance with section 3.1 for the ITT population by treatment groups defined in section 3.7. Medical history will be ordered from the highest frequency in the overall column by SOC and PT.

Medical history listings will be provided by stage and treatment arm (grouping provided in section 3.7) sorted by subject ID for the ITT population, along with ongoing status of medical history and age/sex of the subject.

7.3 Viral Serology

Hepatitis B, Hepatitis C and Human Immunodeficiency Virus (HIV) results will be presented by stage and treatment arm sorted by subject ID for the ITT population.

7.4 Pregnancy

Listing for pregnancy results will be provided by stage sorted by subject ID for the ITT population.

7.5 Follicle Stimulating Hormone Testing

Women not of childbearing potential must be post-menopausal (defined as at least 50 years with cessation of regular menstrual periods for at least 12 months with follicle stimulating hormone > 40 IU/L). Post-menopausal status will be confirmed through testing of FSH levels at Screening. FSH results obtained will be presented in the by-participant data listings only.

7.6 Eligibility

Participant eligibility will be listed in a data listing.

8. TREATMENT EXPOSURE

Treatment exposure (total number of injections, total volume administrated, total Dose administrated) will be summarized using descriptive statistics in accordance with section 3.1 based on the Safety population. All study drug administration information (study drug administered (Yes/No), reason not administered, start and end date and time of administration, Lignocaine application, total volume administrated, total number of injections, study drug given per protocol (Yes; details of administration/ No; Reason not given per protocol) will be presented in the by-participant data listings.

Total administrated dose can be calculated as below:

Total Dose Administrated (mg)= Total Volume Administered (mL) × 5 mg/mL

9. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the most current version of the World Health Organization Drug Dictionary (WHODD). Medications will be mapped to the Anatomical Therapeutic Chemical (ATC) Level 4 and preferred term (PT), as the primary interest for the analysis.

The prior and concomitant medications and therapies are defined as follows.

1. Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study medication.

2. Concomitant Medications: Concomitant medications are defined as any medication (other than the study drug) that was used at least once after the first administration of the study drug. If the end time of the medications is unknown, medications that were stopped on the same date as the first study drug administration will be defined as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

The prior and concomitant medications/therapies are exclusive with each other.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class Level 4 and PT as noted in section 3.1 (categorical descriptive analysis) for the Safety population. Participant who used the same medication on multiple occasions will only be counted once in the specific category (PT). PTs will be sorted alphabetically. In addition to the summaries by the coded terms, the number of participants who used at least one concomitant medication during the study will be presented.

Prior and concomitant medications will be presented in the by-participant data listings for the Safety Population. Listing will include concomitant medications/therapy classification, medication taken, start and end date/time, ongoing status, reason for administration, dose, unit, dose form, frequency, and route of administration.

10. EFFICACY

Efficacy will be analyzed in both Stage 1 and Stage 2 of the study. All ultrasound data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

Stage 1

Efficacy endpoints to be analyzed in Stage 1 are:

1. Reduction of subcutaneous abdominal fat thickness as measured by ultrasound compared with Baseline (Week 4 vs Baseline)
2. Reduction of subcutaneous abdominal fat volume over the treated area as measured by ultrasound compared with Baseline. (Week 4 vs Baseline)

*Note: no efficacy assessments will be done for Group 1 of Stage 1 study. All the information collected for thigh fat thickness will be presented in by-subject listing sorted by subject ID for the ITT population.

- The subcutaneous abdominal fat thickness and fat volume (as defined in section 3.2) at baseline, and Week 4, along with the change and percentage change of fat thickness and fat volume from baseline will be summarized using descriptive statistics in accordance with section 3.1.
- Within-treatment analysis will be performed by paired t-test for Week 4 vs baseline for reduction of subcutaneous fat thickness and fat volume. An estimate of the mean difference in subcutaneous fat thickness and fat volume between baseline and Week 4 along with its 95% CI and corresponding p-value will also be provided. No claim can be made on these p-values based on this efficacy analysis as it is exploratory in nature. These p-values should be used wisely.

The analysis set for the primary efficacy analysis is the ITT population

Stage 2

Primary efficacy endpoints to be analyzed in Stage 2 are:

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

Secondary efficacy endpoints to be analyzed in Stage 2 are:

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

- A summary table presenting the number and proportion of subjects who lose at least 150mL and subjects who lose at least 200 mL of subcutaneous fat volume over the treated area together with two-sided Clopper-Pearson 95% confidence intervals for each treatment group defined in section 3.7 will be produced.
- For the subcutaneous fat volume as measured by ultrasound data, summary statistics (as described in section 3.1) will be presented for values and change from baseline value at each visit.
- If the assumptions met, the Mixed-Effect Model Repeated Measurement (MMRM) will be used to assess the change over time in the CBL-514 and placebo treatment arms for the abdominal subcutaneous fat volume. The assumptions for MMRM can be checked as described in section 16.3. There will not be any alternative method used if assumptions of model-based analysis are not satisfied.

The model will include the following fixed factors/covariates:

- Baseline subcutaneous fat volume,
- Treatment Group,
- Study Visit,
- Treatment Group and Study Visit interaction term;

Subject as random effect and repeated visits will be also included in the model.

Unstructured within-subject covariance structure (TYPE=UN) will be selected for the model initially which makes no assumption about the relationship in the correlation among visits. If it leads to non-convergence, the following covariance structures will be explored: first order autoregressive (AR (1)), Heterogenous Toeplitz, Toeplitz, and compound symmetry, if appropriate. If the model does not converge, alternative covariance structures will be investigated. The Akaike Information Criteria (AIC) will be used to select the best model (smaller is better).
If model does not converge after the above, a standard regression model will be fitted at each time point using the same covariates as described above.

The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom for tests of fixed effects.
Also, if the model is complex, simpler model will be explored.

The LS mean change from baseline, along with corresponding 95% CI and p-values for each treatment arm for Visit 3, Visit 4, Visit 5, Visit 6, and Visit 7 will be presented. In addition, the difference in change from baseline at Visit 6 and Visit 7 for CBL-514 600 mg versus placebo will be provided for the ITT population and repeated for PP Population.

No claim can be made on these p-values based on this efficacy analysis as it is exploratory in nature. These p-values should be used wisely.

The SAS code sample that can be used to implement the above MMRM analysis is given below:

```
PROC MIXED DATA= input_data;
CLASS treat (ref= 'Placebo') visit (ref='Baseline') usubjid;
MODEL chg= base treat visit treat*visit /ddfm=kr Solution CL;
REPEATED visit/subject=usubjid  type=UN;
LSMEANS  treat*visit/pdiff CL alpha=0.05;
LSMENAS visit/cl;
ods output lsmeans=lsmeans diffs=diffs;
run;
```

- The initial visits during which a subject experience a subcutaneous fat volume loss of 150 mL or more will be marked as flagged. For each subject, the number of treatments administered until the first flagged visit will be recorded and summarized descriptively along with the number of injections, volume and dose administrated in accordance with Section 3.1. In cases where the subject is scheduled to receive the study treatment on the same date as the first flagged visit, that treatment will not be included in the count.

All the summary and analysis tables will be done for ITT and PP population for treatment groups defined in section 3.7.

All analyses will be performed without adjustment for multiple endpoints.

11. SAFETY

Safety endpoints will be analyzed using the Safety population. Safety endpoints will be summarized descriptively as described in section 3.1.

11.1 Adverse Events

AEs and serious AEs (SAEs) are defined in the study protocol.

Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred following the first administration of study medication. If missing dates or time prevent a clear determination as to whether the AE is treatment emergent, the adverse event will be regarded TEAE.

All AE verbatim terms will be coded using the most recent version of MedDRA. All AE summaries will be restricted to include TEAEs only. AEs occurring prior to first dose of study medication will be listed but not included in any tabulations. Summary tables will include the number of participants (%) experiencing an event and the number of events. Participants will be counted only once for each SOC and PT level (categorical descriptive analysis).

The TEAE summaries will include:

- Overall summary of TEAEs.
- Summary of TEAEs by SOC, PT and Relationship.
- Summary of TEAEs by SOC, PT and Severity.
- Summary of Definitely Related TEAEs by SOC, PT and Severity
- Summary of Probably or Possibly Related TEAEs by SOC, PT and Severity
- Summary of TEAEs of Special Interest by SOC, PT and Severity
- Summary of serious TEAEs by SOC and PT.
- Summary of Treatment Related serious TEAEs by SOC and PT
- TEAE summary of events leading to the study drug withdrawal by SOC and PT.
- Treatment Related TEAE summary of events leading to the study drug withdrawal by SOC and PT

For the ‘Overall Summary of TEAEs’, the following items will be included:

1. Any TEAEs
2. Any serious TEAEs
3. Any TEAEs leading to study discontinuation
4. Any TEAEs of special interest
5. Any related TEAE
6. Any TEAEs leading to study discontinuation
7. Any TEAEs leading to death

All AEs will be listed and will include the start and stop date and time of AEs, AE number, verbatim term, Preferred Term, System Organ Class, SAE/TEAE flag, actions taken for AE, relationship to study treatment and outcome.

Separate by-participant data listings will be created for SAEs, AEs leading to study discontinuation, and AEs leading to death. These listings will be presented by participant ID and AE start date/time for the Safety Population.

11.2 Safety Laboratory Assessments

Blood and urine samples will be collected at the time points specified in the Schedule of Events (refer to the Protocol) to conduct hematology, chemistry and urinalysis (including microscopic examinations) analyses.

The following tests will be performed within each of the specified test panels:

Hematology:

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

Biochemistry:

1. Urea (U)
2. Creatinine (CREAT)
3. TBIL
4. Albumin (ALB)
5. ALKP (ALP)
6. AST
7. ALT
8. GGT
9. Estimated Glomerular Filtration Rate (eGFR)
10. Glycated hemoglobin (HbA1c)
11. Fasting Blood Sugar (FBS)
12. Sodium (NA)
13. Potassium (K)
14. Chloride (CL)
15. Bicarbonate (BICARB)
16. Triglyceride
17. Total cholesterol

18. LDL-C

19. HDL-C

Coagulation:

20. International Normalized Ratio (INR)

21. Activated Partial Thromboplastin Time (aPTT)

22. Prothrombin Time.

Urinalysis & Microscopic Urinalysis:

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

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

Results for individual parameters may be reported in different units depending on the analyzing laboratory. If required, the results (and the corresponding normal range cut-off values) for individual parameters may be converted to International System of Units (S.I.) units to summarize the data.

For all the parameters where a unit value has been reported, the parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Albumin (g/L)'. For the urinalysis parameters, the parameter name will be the reported test name only. Parameters will be sorted alphabetically within tables and listings.

For all parameters where a normal range limit value was reported, the normal range will be derived based on the available lower and upper limit values and any reported mathematical symbols. If both a lower and upper limit value is available, the normal range will be presented as '(Lower, Upper)'.

The reported results for each parameter with a defined normal range will be classified ('Low', 'Normal', 'High') in relation to the defined normal range limits. If a result is equal to the normal range cut-off value, the result will be considered 'Normal'.

The hematology and chemistry results tables will present summary statistics for each laboratory parameter within the specific test panel. For each parameter, summaries will be presented for the baseline and each scheduled post-baseline visit. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The change from baseline values at each post-baseline visit will be calculated for all parameters with continuous results (except for pH and Specific Gravity). The abnormal urinalysis result (dipstick and microscopy), if applicable, will be listed only.

The decimal precision to which the summaries for each parameter will be based on the maximum number of decimals to which the reported result or the normal range limits are presented to in the raw data. The results and normal ranges will be displayed to the same decimal precision in the listings.

Additionally, counts (%) of number participants with values out of normal range at each scheduled time point will also be presented along with shift tables that will represent the changes in normal range categories across post-baseline time points (categorical descriptive analysis).

The urinalysis table will present counts and percentages of normal, abnormal clinically significant and clinically significant for the reported results at baseline and each post-baseline visit for all parameters (categorical descriptive analysis).

11.3 Vital Signs

The following vital signs measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

1 Pulse Rate (beats/min);

2 Systolic blood pressure (SBP) (mmHg)

3 Diastolic blood pressure (DBP) (mmHg)

4 Respiratory rate (breaths/min)

5 Body temperature (ºC)

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Vital signs measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision to which the summaries for each parameter will presented will be based on the maximum number of decimals to which the results were reported on the eCRF.

11.4 12-Lead Electrocardiogram (ECG)

The following ECG measurements will be taken at the time points specified in the Schedule of Events (refer to the Protocol):

1 Heart Rate (bpm)

2 PR Interval (msec)

3 QT Interval (msec)

4 QTcF Interval (msec)

5 QRS Duration (msec)

6 ECG clinical interpretation

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Ventricular Rate (beats/min)'. Parameters will be sorted in the order that the measurements were collected in on the ECG eCRF page within the tables and listings.

ECG measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

The decimal precision for each parameter will be based on the maximum number of decimals to which the results were reported on the eCRF.

The summary of overall interpretation findings table will present counts and percentages for the reported results at baseline and each post-baseline visit/time point. Result categories will be ordered as 'Normal', 'Abnormal Not Clinically Significant (NCS)' and 'Abnormal Clinically Significant (CS)' (categorical descriptive analysis).

11.5 Physical Examinations

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

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

By-subject data listings will be presented at the time points collected for complete physical examination parameters and Symptom directed physical examination parameters.

11.6 Pregnancy and Follicle Stimulating Hormone (FSH) Tests

All information related to pregnancy testing (urine and serum based) and contraception status will be presented in the by-participant data listings. Follicle stimulating hormone (FSH) test for postmenopausal women will be presented in the data listing.

12. IMMUNOGENICITY

Not Applicable for this study.

13. CHANGES TO THE PLANNED ANALYSIS

Not applicable.

14. INTERIM AND FINAL ANALYSIS

14.1 Interim Analysis

No Interim analysis planned for this study.

14.2 Final Analysis (End of Study)

The final analysis will be conducted after all participants have completed the study, the clinical database has been locked, the analysis populations have been approved and the study has been unblinded.

The final analysis will be based on the final version of SAP. Any deviations from the planned analysis will be documented in the CSR.

15. SOFTWARE

- SAS® Version 9.2 or higher (SAS Institute, Cary, North Carolina, USA).

16. APPEENDIX

16.1 Appendix 1: Schedule of Assessments (Stage 1)

Assessment	Screening	Treatment	Follow-up		
Stage 1	**Screening**	**Day 1***	**Week 1**	**Week 2**	**Week 4**
Day	**-28 to -1**	**1**	**8 ± 4 days**	**15 ± 4 days**	**29 ± 4 days**
Visit	**1**	**2**	**3**	**4/ ET**	**5 /EOS**
Informed Consent	X				
Inclusion/Exclusion	X	X			
Demographics	X				
Medical History and Prior Medications[1]	X				
Subject Diary[2]		X	X	X	X
Anthropometric Parameter[3]	X	X	X[18]	X	X
Abdominal or Thigh Ultrasound[4]	X	X		X[17]	X
Medical Examinations					
Physical Examination[5]	X	X	X[16]	X[16]	
Injection site assessments[6]		X	X	X	X
Vital Signs[7]	X	X	X[16]	X[16]	
ECG[8]	X	X	X[16]	X[16]	
Laboratory Evaluation					
Blood Tests[9]	X	X	X[16]	X[16]	
Urinalysis[10]	X	X	X[16]	X[16]	
Pregnancy Status[11]	X	X		X[16]	
Virology[12]	X				
IP Administration		X			
Photography[13]		X	X	X	X
AE[14]		X	X	X	X
Concomitant Medication		X	X	X	X[15]

AE: Adverse event; AESI: Adverse event of special interest; Ag/Ab: Antigen/antibody; ALP/ALKP: Alkaline phosphatase; ALT: Alanine aminotransferase; aPTT: Activated partial thromboplastin time; AST: aspartate aminotransferase; β-hCG: Beta human chorionic gonadotropin; ECG: Electrocardiogram; eGFR: Estimated glomerular filtration rate; EOT: End of treatment: EOS: End of study; ET: Early Termination; FBS: Fasting blood sugar; GGT: Gamma-glutamyl transferase; Hb: Hemoglobin; HbA1c: Hemoglobin A1c; HBV:

Hepatitis B Virus; Hct: Hematocrit; HCV: Hepatitis C Virus; HDL-C: High-density lipoprotein cholesterol; HIV: Human immunodeficiency virus; INR: International normalized ratio; IP: Investigational product; ISR: Injection site reaction; LDL-C: Low-density lipoprotein cholesterol; RBC: Red blood cell; SAE: Serious adverse event; TBIL: Total bilirubin; WBC: White blood cell; WOCBP: Woman of childbearing potential.

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

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

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

[3] Anthropometric parameters to be collected include body height and body weight. Body height will be measured at Screening only. Thigh circumference will be collected only for Group 1 (320 mg) in Stage 1 study.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

16.2 Appendix 2: Schedule of Assessments (Stage 2)

Assessment/Schedule	Screening	Treatment				Follow-up	
Visit	**1**	**2**	**3**	**4**	**5/EOT**	****6/ET**	**7/EOS**
Day	**-28 to -1**	**1***	**(Visit 2 + 4 weeks)**	**(Visit 3 + 4 weeks)**	**(Visit 4 + 4 weeks)**	**(Visit 5 + 4 weeks)**	**(Visit 5 + 8 weeks)**
Visit window		-	**+ 7days**	**+ 7days**	**+ 7days**	**± 7days**	**± 7days**
Informed Consent	X						
Inclusion/Exclusion	X	X					
Demographics	X						
Medical History and Prior Medications[1]	X						
Subject Diary		X	X	X	X	X[14]	X[14]
Anthropometric Parameter[2]	X	X	X	X	X	X	X
Efficacy Assessment							
Abdominal Ultrasound[3]		X	X	X	X	X	X
9-Point CBL-514 Satisfaction Questionnaire						X	
Medical Examinations							
Physical Examination[4]	X	X[16]	X[16]	X[16]	X[16]	X[16]	X[16]
Injection site assessments[5]		X	X	X	X	X	X
Vital Signs[6]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
ECG[7]	X	X[16]				X[18]	
Laboratory Evaluations							
Blood Tests[8]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
Urinalysis[9]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
Pregnancy Status[10]	X	X[16]	X[16]	X[16]	X[16]	X[16]	
Virology[11]	X						
Photography[12]		X	X	X	X	X	X
Randomization		X					
CBL-514 or Placebo Administration[17]		X	X	X	X		
Adverse Events[13]		X	X	X	X	X	X

Assessment/Schedule	Screening	Treatment				Follow-up	
Visit	**1**	**2**	**3**	**4**	**5/EOT**	****6/ET**	**7/EOS**
Day	**-28 to -1**	**1***	**(Visit 2 + 4 weeks)**	**(Visit 3 + 4 weeks)**	**(Visit 4 + 4 weeks)**	**(Visit 5 + 4 weeks)**	**(Visit 5 + 8 weeks)**
Visit window		**-**	**+ 7days**	**+ 7days**	**+ 7days**	**± 7days**	**± 7days**
Concomitant Medication		X	X	X	X	X	X[15]

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

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

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

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

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

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

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

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

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

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

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

[9] Urinary samples for dipstick will be collected.

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

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

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

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

[14] On follow-up visits, no subject diary will be provided to subjects and only review and recording of subject dairy entries will be conducted.

[15] Collected only if a medication is related to AEs following the Visit 6

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

[17] Eligible subjects will be randomly assigned to either the CBL-514 group or placebo group at a ratio of 2:1.

[18.] ECG assessment can be performed on or within 4 days before or after Visit 6/ET

16.3 Appendix 3: MMRM Assumptions Testing

a) Sphericity assumption

The first assumption of the MMRM analysis is sphericity, posits that the repeated measures of a within-subjects effect should have equal variances and constant covariances.

- When the sphericity assumption is satisfied, the F-test in a standard analysis of variance is appropriate.
- When the sphericity assumption is violated, the F-test in a standard analysis of variance will be positively biased; that is, it will be more likely to make a Type I error (i.e., reject the null hypothesis when it is, in fact, true).
- Violation of sphericity was corrected using the Greenhouse–Geisser method.

b) Normality assumption

Kolmogorov-Smirnov normality test will be used to check normality of the data and the results will be presented.

SAS Proc to be used for normality testing:

```
ods output TestsForNormality = Normal;
proc univariate data=input normal plots;
var CFB; *CFB=Change from baseline;
histogram Diff /normal;
qqplot /normal (mu=est sigma=est);
run;
ods output close;
data Normality;
set Normal (where = (Test = 'Kolmogorov-smirnov'));
if pValue > 0.05 then Status ="Normal";
else Status = "Non-normal";
drop TestLab Stat pType pSign;
run;
```

Perform the following steps to check the normality of data.

1. First, check normality of data by pooling all visits data together if normality is achieved perform the parametric test.
2. If overall data doesn't show normality, check normality at each timepoint and if only few timepoints achieve normality, then still perform parametric test as normality can be assumed for non-normal timepoint.
3. If extreme outliers are present, then remove the outliers and check normality to perform parametric test.
4. Other normality tests result will be explored in case of departure from normality assumption.
5. If normality assumption is still violated, the normality will be assumed to perform parametric tests.

c) Test for Homoscedasticity

Homogeneity of variances between two treatment groups will be tested using Levene's test.

```
proc glm;
class treat;
model CHG = treat;
means treat / hovtest=levene welch;
run;
```

Note that only the results from the HOVTEST= and WELCH options in PROC GLM account for variance heterogeneity. All other results assume equal variances. If heteroscedasticity occurs, all the results will be adjusted for unequal variances by adding the DDFM=SATTERTHWAITE option in the MODEL statement to adjusts the degrees of freedom for the unequal variances.

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18. REFERENCES

1) Clinical Study Protocol Version 8.0 dated 1 March 2023.