RZL-012 Study Protocol

Protocol Number RZL-012-P2aUS-001.4

A Double Blind, Randomized, Placebo Controlled, Dose Escalation Phase 2a Clinical Trial for the Evaluation of Safety and Thermogenesis-induction of RZL-012 in Overweight and Obese Volunteers

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
BAT	Brown-like adipose tissue
BMI	Body Mass Index
BUN	Blood urea nitrogen
°C	Degrees Celsius
CBC	Complete blood count
CDC	Center for Disease Control
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CK-MM	Creatine Kinase - Muscle
C_{max}	Maximum observed concentration
CNS	Clinically not significant
CRF	Case Report Form
CPK	Creatine phosphokinase
CRP	C-reactive protein
CS	Clinically significant
CTC	Common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
DICOM	Digital Imaging and Communications in Medicine
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EF	Efficacy analysis set
ER	Emergency room
FDA	Food and Drug Administration
FFA	Free fatty acids
FIFO	First In First Out
FLASH	Fast-low-angle shot

Abbreviation or Specialist Term	Explanation
FOB	Functional Observational Battery
GLP	Good Laboratory Practice
GTTP	Gamma-glutamyltransferase
HBV	Hepatitis B virus
HCRC	Hadassah Clinical Research Center
HCV	Hepatitis C virus
H&E	Hematoxylin and eosin stain
HDL	High-density lipoprotein
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LDH	Lactate dehydrogenase
LPL	Lipoprotein lipase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP	Monocyte chemoattractant protein
MCV	Mean corpuscular volume
MD	Medical Doctor
MPV	Mean platelet volume
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
NSAIDs	Non Steroid Anti-Inflammatory Drugs
PI	Principal Investigator
PK	Pharmacokinetics
PKA	PK Analysis set
PT	Prothrombin time
PTT	Partial thromboplastin time

Abbreviation or Specialist Term	Explanation
RBC	Red blood cells
RDW	Red cell distribution width
SA	Safety analysis set
SAE	Serious adverse event
SAT	Subcutaneous adipose tissue
SC	Subcutaneous
SFM	Subcutaneous fat mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal half-life
TAG	Triacylglycerols
TBD	To be determined
TC	Total Cholesterol
TG	Triglycerides
TGF	Transforming growth factor
T_{max}	Time of maximum observed sample concentration
TNF	Tumor necrosis factor
UCP1	Uncoupling protein 1
ULN	Upper limit of normal
US/USA	United States/United States of America
WAT	White adipose tissue
WBC	White blood cells
WHR	Waist to hip ratio

STATEMENT OF COMPLIANCE

This clinical trial will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice E6 and the applicable regulatory requirements.

INVESTIGATOR SIGNATURE PAGE

I have read and understood the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP).

I will provide adequate protocol training to my associates, colleagues and employees assisting in the conduct of the study.

I will obtain Institutional Biosafety Committee (or equivalent) and Institutional Review Board (IRB)/Ethics Committee (EC) approval of the protocol and the Subject Informed Consent form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the Institutional Biosafety Committee (or equivalent) and IRB/EC except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed Subject Informed Consent form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event that occurs during the course of the study in accordance with the procedures described in Section 9 of the protocol.

I will allow the Sponsor, Raziel Therapeutics Ltd. and its agents, as well as the United States (US) Food and Drug Administration (FDA) and other regulatory agencies, to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than one week).

Investigator's name	Investigator’s Signature	Date

PROTOCOL SYNOPSIS

Protocol Number	RZL-012-P2aUS-001.2
Protocol Title	A Double Blind, Randomized, Placebo Controlled, Dose Escalation Phase 2a Clinical Trial for the Evaluation of Safety and Thermogenesis-induction of RZL-012 in Overweight and Obese Volunteers
Study Phase	Phase 2a
Study Drug	RZL-012
Study Objectives	Primary objective: Evaluation of the overall safety and preliminary efficacy of RZL-012 after injection into the subcutaneous fat. Secondary objective: Determination of RZL-012 pharmacodynamics and pharmacokinetics. Evaluation of the existence of a thermogenic effect and the extent, duration and tissue associated changes of the thermogenic response to RZL-012, via minimal invasive means (injected-site thermogenesis imaging, Magnetic Resonance Imaging (MRI) and biopsy) after subcutaneous injection into fatty tissue below the skin.
Sample Size	32 subjects
Study Design	This is a consecutive 4 cohort, dose escalation placebo-controlled clinical trial in overweight and obese subjects. All cohorts will be comprised of 6 active (RZL-012) and 2 placebo subjects. Within each cohort, dosing of the first 3 subjects will progress consecutively from one individual to the other at 7-day intervals. For additional precaution, the first 3 subjects will be forced randomized into 2 active and 1 control. This study design will allow the physicians to monitor safety in a two subjects at each dose, nevertheless the blindness will remain intact. The remaining subjects in a cohort will be randomized to either active treatment or placebo in a ratio determined by the number of subjects targeted for each cohort. Dosing of the next subjects will be in couples and the last subjects will be in a triplet. If intolerable side effects in a cohort occurs, dosing will progress subject by subject, rather than in couples or triplet. The trial will proceed within a cohort and from one cohort to the next as long as no more than one subject experiences intolerable side effects in the lower-dose cohort, and based on the decision made by a Data and Safety Monitoring Board (DSMB). The decision to proceed to the next cohort will be made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject in each cohort. If two (2) intolerable side effects are observed in any dose cohort, further treatment at that dose will be stopped and only tolerable doses used for further subjects. The DSMB will be comprised of two independent MDs expert in early phase clinical trials.
Study Population	20-60 years old, overweight and obese by Body Mass Index (BMI) definition ($27.5 < BMI \leq 34.9$), adult males.

Main Inclusion Criteria	Subjects must meet all the following to be eligible for study participation: 1. Adult male subjects, 20-60 years old. 2. Subject is considered overweight and obese, with 27.5 < BMI ≤ 34.9. 3. Significant subcutaneous abdominal fat as defined by Waist to hip ratio (WHR) ≥ 0.9. 4. Subjects with stable weight in the last 3 months by medical history. 5. Not one of the following eating disorders by subject's declaration: anorexia nervosa, bulimia nervosa. 6. Generally considered healthy according to medical history, physical examination, electrocardiogram (ECG) and laboratory evaluation with a special emphasis on metabolic parameters (fasting glucose concentration < 100 mg, normal blood pressure). 7. Subject is willing to refrain from sexual activity or agrees to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012. 8. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study. 9. Subjects must sign an informed consent indicating that they are aware of the investigational nature of the study.
Main Exclusion Criteria	Subjects meeting any of the following criteria will be excluded: 1. Subjects weighing less than 75 kg. 2. Subjects who have reduced/gained weight more than 5% of their current body weight in the last 3 months. 3. Unable to tolerate subcutaneous injection. 4. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator put the subject at significant risk, are not eligible. 5. Subjects who test positive to either Hepatitis B virus (HBV), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV) are not eligible. 6. Subjects with a clinical history of primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids are ineligible. 7. As a result of medical review, physical examination, the PI (or medically qualified nominee) considers the subject unfit for the study. 8. Medication use on regular basis including blood and blood products. 9. Positive drug and alcohol tests. 10. Known sensitivity to components of the injection formulation. 11. Prior wound, tattoo or infection in the treated area. 12. Excessive growth of hair in the abdomen region. 13. Claustrophobia or MRI incompatible device or implant.

Intolerable Side Effect Definition

Safety will be the principal primary endpoint of this study, as such if there are 2 intolerable and at least possibly related side effects observed in any dose cohort, that dose cohort will be stopped and only tolerable doses used for future subjects

An intolerable side effect defined as any of the following treatment-related adverse drug reactions (ADRs):

- Any Grade 3 or greater event except for the following (For the following entities, a discussion will be held by the PI, DSMB and Sponsor to decide whether considered as:intolerable side effects):
  - Flu-like symptoms and fever that responds to standard treatment within 72 hours
  - Localized edema and erythema
  - Pruritus
  - Pain
  - Skin/soft tissue inflammation
  - Fat Atrophy
  - Liver enzymes abnormality
  - Non-significant lab abnormalities, lasting less than 7 days (see Section 3.3.2)

Study discontinuation is to be considered by the investigator in any case of an intolerable side effect, and the actions taken are to be fully documented in source documents and Case Report Forms (CRFs).

To be considered an intolerable side effect, such an event must be considered to be possibly or probably related to the study drug

Subjects experiencing an intolerable side effect will be withdrawn from the study, but followed for toxicity.

The study may also be prematurely terminated in any of the following cases:

- Recurring serious or severe adverse drug reaction (ADR) clinically evaluated by DSMB as warranting study termination.
- A decision made by Sponsor and/or IRB/EC and/or local regulatory agency to terminate the study.

Study Drug Dosage and Administration

Subjects will receive single doses of the investigational product (RZL-012) or the placebo in accordance with the following:

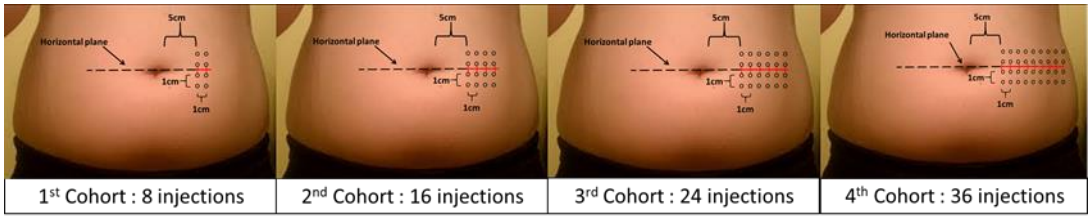
	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Number of Subjects – Active/Placebo	6/2	6/2	6/2	6/2
Total Dose RZL-012 (mg)	40	80	120	180
Dose per NOAEL*	1/6.25th	1/3.125th	1/2.34th	1/1.39
Number of Injections	8	16	24	36

* based on Human Equivalent Dose (HED) from GLP toxicology study)

The initial dose will be 40 mg RZL-012 (1/6.25th the no observed adverse effect level (NOAEL) based on Human Equivalent Dose (HED) from GLP toxicology study) with subsequent doses of 80 mg and 120 mg (1/3.125th and 1/2.34^{h} the NOAEL based on HED). The final dose will be 180 mg RZL-012, (1/1.39the NOAEL based on HED). Subjects will receive a single treatment in multiple sites (8-48) of injection diagonally (45 °) to the skin surface at 5 cm lateral to the umbilicus lateral wall. The distance between injected sites will be 2 cm (see picture below) in the first three cohorts and 1cm in the fourth cohort.

The first cohort of 6 subjects will receive 8 injections (0.1 mL each in a 2 x 4 cluster and 2 cm apart) of 40 mg RZL-012 (~1/6.25th of the NOAEL). Additional 2 subjects in the cohort will serve as control and will be injected placebo (vehicle).

If no more than 1 subject experiences intolerable side effects within 14 days following the injection of the last dosed subject, according to schedule and following the DSMB approval an additional cohort (Cohort 2) of six volunteers, as above, will receive 16 injections (0.1 mL each in a 4x4 cluster and

	2 cm apart) adding up to 80 mg RZL-012 (~1/3.125th of the NOAEL). Additional 2 subjects in the cohort will serve as control and will be injected placebo (vehicle). If no more than 1 subject experiences intolerable side effects within 14 days following the injection of the last dosed subject according to schedule and following the DSMB approval, an additional cohort (Cohort 3) of six volunteers will receive a cluster of 24 injections (0.1 mL each in a 6x4 cluster and 2 cm apart) adding up to 120 mg RZL-012 (~1/2.34th of the NOAEL). Additional 2 subjects in the cohort will serve as control and will be injected placebo (vehicle). If no more than 1 subject experiences intolerable side effects within 14 days following the injection of the last dosed subject according to schedule and following the DSMB approval an additional cohort (Cohort 4) of six volunteers, as above, will receive 36 injections (0.1 mL each in a 9x4 cluster and 1cm apart) adding up to 240 mg RZL-012 (~1/1.39 of the NOAEL).. Additional 2 subjects in the cohort will serve as control and will be injected placebo (vehicle).  1st Cohort : 8 injections | 2nd Cohort : 16 injections | 3rd Cohort : 24 injections | 4th Cohort : 36 injections
Concomitant Medication	All concomitant medication given 3 months prior to study entry, including blood and blood products, dietary supplements, and non-prescription drugs will be listed at screening/baseline. The clinical significance of the medication use will be decided by the investigator. Study subjects will be routinely questioned for changes in the administration of concomitant medication during the trial. Subjects may not receive the following medications while on study: • Chronic treatment with systemic steroids or immunosuppressive drugs. • Chronic treatment with Non Steroid Anti-Inflammatory Drugs (NSAIDs). • Any investigational product other than RZL-012. Before dosing, analgesic gels or creams such Lidocaine (e.g., Emla) or Pramoxine should be used to numb the injected site. An ice pack may be applied on the site of injection following dosing to help reduce pain. At day 3 following blood sampling for histamine, the anti-histamine Benadryl Gel (Dimethindene Maleate 0.1 %) for topical use only should be initiated prophylactically, according to drug instructions for use to avoid itching in the injected area. Benadryl Gel should be applied for 7 days. Use of supplements or complementary medicines/botanicals is prohibited, except for conventional multivitamin supplements.
Study Procedure	Study activities upon study entry will include, but not be limited to: Informed Consent, full medical history, physical examination, anthropometric measurements, vital signs measurements, ECGs, clinical laboratory tests, photography, thermal imaging and skin irritancy evaluation of site injection. Subjects will be randomized upon eligibility to RZL-012 or placebo and to a right side or left side injection according to a predefined randomization scheme. Periodical site visits will allow assessment of treatment safety and efficacy. Subjects will be advised to keep their regular diet and physical activity.
Visit Schedule (See Table 2)	Subject site visits will be performed ± 1 days from scheduled date for study visits Day 0-28 and 2± 1 days from schedule date for follow-up visits (Day 56-168). All data relevant for the visit needs to be obtained within 3 days (e.g., blood tests results) of visit. **Screening Day 1 visit (Day -28 through -7):** - Following signing the informed consent - assessment of subject eligibility will include: medical history, physical examination, anthropometric measurements (BMI, WHR), vital

signs, ECG, serology assays (HBV, HCV and HIV), clinical laboratory tests, drug screen. Subjects should come fasting (10-12 hr. fast) for the glucose and weight measurement.

Clinical laboratory tests will include:

1. Hematology: Complete blood count (CBC including White blood cell [WBC] differential values), Fibrinogen, D-dimer, and coagulation (International normalized ratio [INR], Partial thromboplastin time [PTT] and Prothrombin time (PT).).
2. Serum chemistry analysis: sodium, calcium, potassium, phosphorus, glucose, liver enzymes (Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], Lactate dehydrogenase [LDH], Creatine-kinase MM [CK-MM], Gamma-glutamyltransferase [GTTP], Alkaline phosphatase [ALP]), Bilirubin, Creatinine, Urea/Blood urea nitrogen [BUN[, Total protein, Albumin, Amylase, Creatine phosphokinase [CPK] and Leptin.
3. Urinalysis: Nitrite, Sodium, Potassium, Calcium, Phosphate, Protein, RBC, WBC, Blood, Glucose, Ketone bodies, Bilirubin, Urobilirubin, Urine specific gravity, Osmolarity, and pH.

- In addition, photography, infra-red imaging and evaluation of skin irritancy by Draize score of the injection site area and contra-lateral area.

The relevance of RZL-012 for human treatment of obesity will be assessed by the monitoring of injected-site thermogenesis, utilizing infra-red imaging. Thermal imaging with a sensitive (± 0.1 °C) Infra-Red thermal camera (FLIR A310) will include: a view of the injected area and the contra-lateral non-injected area – at a distance of 1 meter and in a horizontal line from the umbilicus. The thermal camera can create a visual heat map of skin temperatures in real time with a precision of ± 0.1 °C.

Screening Day 2 visit (Day -14 through -2):

- Subjects should come fasting (10-12hr. fast) for weight measurement and MRI scan.
- MRI of 16 slices that include the injected site, for subcutaneous adipose tissue (SAT) evaluation.
- Anthropometric measurements (BMI, WHR).

Clinic Admission visit (Day -1):

- Subject should come fasting (10-12 hr. fast) for weight measurement and for laboratory tests of: glucose, insulin and lipid profile.
  Lipid profile will include: Triglycerides [TG], High-density lipoprotein [HDL], Low-density lipoprotein [LDL], Total-cholesterol [TC] and Free fatty acids [FFA].
- Inflammatory markers and cytokines – Testing from the 2nd, 3rd and 4th cohorts (on 6 RZL-012 treated and 2 placebo treated subjects in each cohort): CRP, Adiponectin, CD-163, Interleukin [IL]-1β, IL-4, IL-6, IL-10, IL12p70, IL-13, IL-23, Tumor necrosis factor [TNF] α and transforming growth factor [TGF] β1.
- Medical history, BMI, WHR, urine drug test, infra-red thermal imaging of the injected area and the contra-lateral side. Blood sample for histamine, serum chemistry and hematology baseline level.

Baseline visit (Day 0):

- Baseline visit will be in an in-patient setting. Subjects will be interned in the study site for visit baseline till the following day.
- Pre-treatment: eligibility confirmation, randomization, vital signs, Draize score, First blood sample for pharmacokinetics will be taken.
- Treatment - All injections will be administered 45 ° to the skin surface using a 1 mL Luer-lock syringe and a 30 G x 1/2" needle (the hole of the needle pointing into the fat layer). The first injection site will be at 5 cm lateral to the umbilicus lateral wall into the left or right abdominal subcutaneous fat.
- Post treatment: ECG (4h and 12h ± 30min post injection), pulse rate (1h, 2h, 4h, 8h, 12h, 24h post injection in the opposite hand of blood sampling), vital signs (2h ± 30 min post injection), Draize score (2h post injection ± 30 min), adverse events (AEs) will be recorded and pharmacokinetics.

Pharmacokinetics with cohorts 1-4– RZL-012 half-life was determined to be 5 hours in the exploratory phase 0 clinical trial (protocol RZL012-P0US-001.3), therefore blood samples will be taken after injection at the given time points: 0, 30, 60 min, 2h, 3h, 4h, 6h, 8h, 12h, 16h,24h, 30h.

Schedule visits (Day 1-28):

- Day 1 following treatment will include: ECG, vital signs including pulse rate, Draize score, photographs and thermal imaging of the treated area. Last 2 blood sample for pharmacokinetics and blood sample for histamine (24hr ± 2hr following injection) will be taken.
- For safety reasons 24hr ± 2hr following injection, Blood samples for serum chemistry and hematology will be taken
- Day 3 following treatment will include Serum chemistry, hematology and histamine. Subjects will start applying an anti-histamine gel.
- Visits will take place every 7 days ± 1d from treatment till Day 28. On study visit Day 28 subject will come fasting (10-12hr fast) for the glucose and lipid profile tests. During visits all tests (physical exam, vital signs, anthropometric measurements, ECG, clinical laboratory tests, urinalysis, fasting glucose and insulin, lipid profile, FFA, inflammatory markers and cytokines, histamine, Draize score, photographs, thermal imaging and MRI will be performed according to schedule (Table 2).
- Subjects will be questioned for adverse events every visit.
- Subjects will record their weight following 8-12hr fast (overnight) and at bedtime once a week (days 7, 14 and 21) in a diary. Diaries will be checked and data will be captured in the CRFs.

Follow-up visits (Day 29-168):

Subjects of the 1st and 2nd cohorts:

- On visit Day 56 - will come after overnight fast (10-12hr fast) for the glucose, insulin, lipid profile tests and FFA levels. Subjects will be followed up for anthropometric measurements, thermal imaging and adverse events. An MRI scan will be conducted on Day 56 in subjects of the 2nd cohort.
- Will continue to be followed for safety every 28 days till Day 112. If Draize-score is 0 for edema and erythema by visit Day 56 then subjects will be followed by phone call for AE.

Subjects of the 3rd and 4th cohorts (or treated with the highest dose achieved):

- Will be followed up for anthropometric measurements (e.g., BMI, WHR) every 28 days as long as the thermogenic effect is apparent and for a period that will not exceed 6 months from the beginning of treatment.
- Subjects will record their weight following 10-12hr fast (overnight) fast and at bedtime once a week when not visiting the site, in a diary. Diaries will be checked and data will be captured in the CRFs.
- In addition, evaluation of the injected area and the contra-lateral side will be performed by Draize score, photographs and thermal imaging
- Subjects will come fasting (10-12hr fast) for the glucose, insulin, lipid profile tests and FFA levels.
- MRI of 16 slices that includes the injected site (SAT evaluation). MRI will be conducted on Day 28 days and every 28 days for a period that will not exceed 6 months from the beginning of treatment in the 3rd and 4th cohorts.
- On Day 56 (following MRI), in 3 randomly selected subjects treated with the 3rd cohort (2 RZL-012 treated that show a sustained thermogenic effect by thermal camera imaging and one subject treated with vehicle with no thermogenic effect), an abdominal subcutaneous (SC) adipose tissue biopsy will be taken from the injected side. The biopsy site will be anesthetized with 1% lidocaine and will be performed by a trained medical professional. The sample (an elliptical excision of 15-20mm deep and 4.5-6cm long) will be placed in a vial filled with a fixation solution (formaldehyde). After 24h ± 2h, the fixation solution should be exchanged to ethanol 80% and further processed for histological analysis. Biopsies will be stained for hematoxylin and eosin (H&E) and further evaluated for BAT

	markers and morphometry. Subjects will be followed 7 days post biopsy and will terminate their study participation. Subjects of the 3rd and 4th cohorts or subjects of the highest dose achieved will be followed up for additional 5 months for safety and efficacy. In case of termination before study day 112 in these 2 cohorts, subjects will be followed for safety as the first cohorts. Subjects of all other cohort will be followed for safety additional 3 months.
Safety Analysis	Safety data from the study will be summarized descriptively by treatment and cohort. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. The nature, frequency, seriousness, severity and relation to study drug of adverse events (AE) will be tabulated for all subjects combined and by treatment. Change-from-baseline values for vital signs, clinical laboratory and ECG will be summarized. Shift tables of normal / abnormal versus baseline may be presented as well. Draize scores will be presented in tabular format by visit, treatment, and cohort. Serious adverse events (SAEs) will be described in narratives as part of the study report.
Study Endpoints	**Primary Endpoint**: Safety: The main objective is the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat. Therefore, the primary safety endpoint will be the incidence of intolerable side effects and all adverse events of RZL-012 injection into the subcutaneous fat. The dose escalation scheme will be stopped if at any dose cohort, 2 patients will experience intolerable side effects. Efficacy: The primary endpoint for efficacy is a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera. A thermogenic effect is defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the non-injected site, apparent at least 28 days after injection and non-related to inflammatory response as determined by inflammatory cytokines. The primary efficacy evaluation will be supported by results from secondary endpoints, including MRI, biopsy and biomarkers. **Secondary Endpoints**: 1. Duration of the thermogenic effect, defined as a net-delta ≥ 1. 2. Local reduction in fat mass as determined by MRI. 3. Clinical laboratory changes from baseline, including improvement in fasting blood glucose and lipid profile. 4. Establishing pharmacokinetic profile for RZL-012. 5. Anthropometric changes from baseline, including body weight change. 6. Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site. 7. Change from baseline in inflammatory markers and cytokines.

Sample Size	This study is planned as a dose escalation study following a 6 subjects per dose group paradigm with the addition of a 2 subjects vehicle control group, for all doses. A maximum of 32 evaluable subjects will be included in the study (24 in the RZL-012 treatment arm and 8 in the placebo arm) and followed for as long as 3 months in the 2 lowest dose cohorts, and in the 2 highest dose cohorts for up to 6 months
Statistical Methods	Statistical analyses will be mainly descriptive in nature where study data will be tabulated and summarized using the mean, standard deviation or standard error, median, minimum, maximum and number of subjects by cohort for continuous data. For categorical data, results will be summarized via a count and percentage by cohort. The effects of noncompliance, dropouts, and covariates, may be assessed to determine the impact on the general applicability of results from this study. If any statistical tests are performed, they will be two-sided. The required significance level of findings will be equal to or lower than 5%. Nominal p-values will be presented. Where confidence limits are appropriate, the confidence level will be 95%. Incidence of intolerable side effects will be tabulated by study drug by cohort along with 95% confidence intervals. The average temperature will be presented in a tabular form by visit, site (treated / not treated) and treatment received (RZL-012 / placebo) by cohort and overall. Difference between the sites (treated – not treated) will be presented in a tabular form by visit treatment along with the change from baseline (net-delta) in these differences by cohort and overall. Non-parametric tests will be used to compare the net-delta between the study arms for the relevant cohorts and visits. AEs and tolerability data will be presented descriptively by treatment and cohort. AEs will be tabulated by body system, preferred term, seriousness, severity and relation to study drug by cohort. Where applicable, changes in values over time (e.g., lab values, vital signs, electrocardiograms [ECGs]) will be presented, this will include clinical laboratory evaluations (including CBC, blood chemistry and urinalysis), coagulation (INR, PTT, PT), cytokines, vital signs, and ECGs. Shift tables of normal / abnormal versus baseline may be presented as well. Draize scores will be presented in tabular format by visit, treatment, and cohort
Study Duration	Study duration is 6.5 months, including enrollment, treatment and follow-up period. Each subject will participate in the study for a up to 42 days as part of this protocol with an extension for up to 3 additional months for safety and 5 additional months for those subjects in the highest dose cohort or subjects in the 3rd and 4th cohort as long as a thermogenic effect is evident.
Study Site	Spaulding Clinical Research LLC, West Bent, Winsconsin

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

The prevalence of obesity continues to escalate worldwide and is becoming one of the most significant global health problems in the United States. Obesity-related co-morbidities place a significant burden on the healthcare system and include type 2 diabetes, hypertension, cardiovascular disease and cancer. While diet and exercise are the primary methods to help control weight gain, in many cases people either cannot or do not want to comply with recommendations for exercise and proper food consumption. These persons who become obese may be candidates for pharmacologic or surgical interventions to help lose weight and prevent or reduce the impact of adverse health consequences. Conventional preventive measures (i.e., diet, exercise, behavioral counseling) and current adjunctive pharmacotherapies have limited efficacy and often fail to provide long term solutions. Few medications are available for the treatment of obesity and their treatment strategies are based on decreasing energy uptake by either appetite suppression or by impaired food absorption. At present, the only FDA-approved drugs for the long-term treatment of obesity are Orlistat (Xenical), Lorcaserin (Belviq), and the combination of phentermine and extended-release Topiramate (Qsymia), as well as GLP-1 analogs.

Orlistat - blocks the action of pancreatic lipase, reducing triglyceride digestion and, thus, absorption. The drug may reduce absorption of some fat-soluble vitamins (A, D, E, and K) and beta-carotene, as well as absorption of some medications. Adverse effects include flatulence, fatty/oily stool, increased defecation, and fecal incontinence.

Lorcaserin - was approved by the FDA in June 2012 as an adjunct to a reduced-calorie diet and exercise for long-term weight management in individuals with an initial BMI of 30 kg/m^2 or higher (obese) or 27 kg/m^2 or higher (overweight) with at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus). Lorcaserin is a schedule IV substance, since it has potential for abuse. Lorcaserin is thought to decrease food consumption and promote satiety by selectively activating 5-HT2C receptors on anorexigenic pro-opiomelanocortin neurons in the hypothalamus. Lorcaserin should be used with caution in patients with heart failure, and it has not been studied in patients with serious valvular heart disease.

Liraglutide - is a glucagon like peptide-1 (GLP-1) analog. GLP-1 is a physiological regulator of appetite and calorie intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. Liraglutide is approved for chronic weight management as an adjunct to diet and exercise in adults with a BMI of ≥ 30 (obese) or adults with a BMI of ≥ 27 (overweight) who have at least 1 weight-related condition (e.g., hypertension, type 2 diabetes, dyslipidemia).

Phentermine and topiramate -The combination of phentermine and extended-release topiramate was approved by the FDA in July 2012 as an adjunct to a reduced-calorie diet and exercise for long-term weight management in individuals with an initial BMI of 30 kg/m^2 or higher (obese) or 27 kg/m^2 or higher (overweight) with at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus). Topiramate, which was first licensed as an adjunctive antiepileptic agent, has been associated with profound weight loss (an average of 5-7% of initial weight). The amount of weight loss appears to be greater with higher baseline weights. The exact mechanism of this effect is being actively investigated. Although the degree of efficacy is exciting, the propensity for adverse effects, especially the central nervous system effects such as drowsiness, paresthesias, memory loss, and confusion, is cause for concern. Qsymia contains an extended-release form of topiramate.

Collectively, that the effect of these medications is limited to 5% - 7% weight loss of the initial body weight after 1 year and is associated with significant side effects.

Bariatric surgery is a drastic intervention, suitable for only a small fraction of the qualifying obese population. Thus, at present, obesity constitutes an outstanding unmet medical need. The World Health Organization has recently released a report on the significant concerns with obesity worldwide that clearly outlines the significant consequences and epidemic scale of the health problem facing mankind (1).

Obesity is a direct result of food-intake in excess of body energy expenditure. Therefore, a feasible approach to combat obesity is via energy-consuming activities, such as physical exercise. Unfortunately, our modern society is moving in the other direction, spending more time in immobilized positions, at work and at home. An alternative strategy for the induction of increased energy expenditure is via the activation of brown adipose-tissue (BAT). Diametric to the common white-adipose-tissue (WAT), which stores energy, BAT burns it. Thus, BAT-associated thermogenesis can counterbalance obesity. For a comprehensive review of the subject see reference (2). BAT existence in humans has only been recently discovered; it is relatively scarce and requires hypothalamic hardwiring for its activation, e.g., upon exposure to low temperatures. It was also found that under certain conditions; WAT could give rise to BAT-like cells functionally identical to BAT, namely, utilizing fat to produce heat. These BAT-like cells are called brite or beige adipocytes. Research labs are currently exploring a variety of experimental approaches to BAT or brite/beige activation (3) but none have an FDA-approved indication for the treatment of obesity.

Moreover, it was discovered that under certain conditions, genuine WAT can become thermogenic, independent of BAT-related mechanisms and unrelated to brite/beige (cells with BAT phenotype, but derived from WAT). It is well understood that BAT thermogenesis depends on up regulation of uncoupling protein 1 (UCP1). This protein takes advantage of the proton gradient generated by the mitochondria and diverts it for heat production, thereby uncoupling oxidative phosphorylation. Indeed, UCP1-defficient mice have defective BAT and are very sensitive to acute cold exposure. However, it was also found that if such UCP1-null mice are

gradually shifted to low temperature, their WAT becomes thermogenic (4). Moreover, UCP1-deficient mice are actually resistant to diet-induced obesity (5). Namely, in the absence of UCP1, the mouse is forced to use alternative thermogenic metabolic systems. However, the spectrum of physiological or biochemical stimuli that can lead to such WAT thermogenic phenotype, have yet to be explored (6). Although these studies were carried out in rodents, there are indications that WAT conversion into a thermogenic tissue exists in humans (7).

Raziel Therapeutics has discovered that a novel synthetic molecule can convert WAT into BAT-like, thereby activating thermogenesis at targeted anatomical sites. A single injection of this compound, called RZL-012, into WAT, is sufficient to trigger outstanding tissue remodeling. This chain reaction begins with removal of WAT adipocytes by macrophages, with ensuing increased vascularization at the treated site and concomitant appearance of BAT-like adipocytes. Temperature measurements of the treated site reveal a persistent local increase in body temperature.

In essence, Raziel Therapeutics technology enables de-novo generation of thermogenic tissue at favorable anatomical sites. Thus, Raziel Therapeutics intends to treat obesity via the induction of BAT-like thermogenic foci in subcutaneous fat. As a result, the extra fat accumulated in obese persons will be turned into heat.

The overall clinical plan for RZL-012 includes the completed exploratory (phase 0) study to evaluate the safety, thermogenesis, and pharmacodynamic response to RZL-012. The additional phase 2 study will be initiated to explore higher doses prior to the initiation of larger studies. The initial exploratory study (Study RZL-012-P0US-001.3) demonstrated that RZL-012 was well tolerated with no serious adverse events reported and that thermogenesis was evident at the injection site of RZL-012-treated subjects. The current study will be in overweight and obese subjects to confirm the safety and pharmacodynamic effects of RZL-012 for the treatment of obesity.

1.1.2. RZL-012 Formulation Development

The active ingredient RZL-012 drug substance was manufactured by Pharmacore. The drug product, 5 % RZL-012 in F12 liquid formulation (RZL-012 in F12 is 5 g/vial, RZL-012 is 250 mg/vial) was manufactured and packed at Nextar Ltd, Ness-Ziona, Israel. RZL-012 in F12 which was once defined as RZL-012 F12 is now defined as RZL-012. The active ingredient and formulation manufacturing and packing were in accordance with current Good Manufacturing Practices (cGMPs).

1.2. NONCLINICAL ASSESSMENTS

1.2.1. Pharmacology

Studies in rats and pigs concluded that RZL-012 triggers remodeling of WAT to BAT-like tissue thereby activating thermogenesis. The dose of RZL-012 to be used in clinical trials was extrapolated from the safety data obtained during animal testing (NOAEL).

1.2.1.1. Efficacy In-vivo and In-vitro Studies

Nonclinical studies were conducted to prove the efficacy of RZL-012 in several in-vivo and in-vitro models.

The in vivo studies (in pigs and rats) involving local administration of RZL-012, focused on two main endpoints: fat tissue reduction and conversion of WAT to brown-like adipose tissue, measured by several parameters, including;

1. Subcutaneous or epididymal fat reduction following RZL-012 treatment.
2. Fat tissue remodeling involving non-inflammatory liponecrosis, followed by tissue "browning", where WAT is converted to brown-like adipose tissue. This conversion can be determined by:
    a. *Histological fat tissue changes:* While white adipocytes are large and resemble a single large oil drop, with a characteristic condensed nucleus, the cells of brown adipose tissue are smaller, contain multiple mitochondria and a euchromatic nucleus.
    b. *UCP-1 levels:* UCP-1 is a mitochondrial inner membrane protein present in BAT that can dissipate the proton gradient before it can be used to provide the energy for oxidative phosphorylation. UCP-1 normally does not exist in WAT.
3. Assessment of body-surface temperature: Classical brown-like adipose tissue is typified by futile burning of fatty acids (i.e., heat production instead of adenosine triphosphate (ATP)), which can be assessed with an infrared camera that can sense differences in body surface temperature.

The objective of the in-vitro studies was to reveal the mechanism of action of RZL-012 in adipocytes. Studies were conducted on the 3T3-L1 adipocytes line, which is considered a model for white adipose tissue.

1.2.1.2. Safety Pharmacology

The effect of RZL-012 on the central and peripheral nervous systems was evaluated using the Functional Observational Battery (FOB) in male Sprague Dawley rats. RZL-012 was administered subcutaneously to rats (n = 8/group) as 10 mg/rat. From the results it was

concluded that RZL-012 did not affect any of the central nervous system functions tested using functional observation battery in rats.

The effect of RZL-012 was evaluated on respiratory functions in male Sprague Dawley rat using head-out plethysmography. RZL-012 was administered subcutaneously at a fixed dose of 10 recorded to cover the entire predetermined time points; Pre-dose, 1, 2, 3, and 4 h post dose. RZL-012 did not affect any of the parameters tested hence it was concluded that RZL-012 has no effects on the respiratory system at the tested dose of 10 mg/rat.

A board-certified veterinary cardiologist conducted a qualitative and quantitative review of the electrocardiograms obtained pretest, pre-dose, 4 and 24 hours post-dose following the subcutaneous injection of 500 mg 5.0 % RZL-012 or vehicle in Domestic Yorkshire Crossbred Swine. There was no effect of the subcutaneous injection of 5.0 % RZL-012 on qualitative or quantitative ECG parameters or blood pressure.

1.2.2. Toxicology

The study design was to evaluate the safety of RZL-012 according to FDA guidelines for Exploratory IND appropriate for first-in-man clinical trial. An extended single-dose toxicity study was performed according to FDA guidance in two species (rat and pig) to establish the NOAEL.

1.2.2.1. Extended Single Dose Toxicity Studies

1.2.2.1.1. Rats

Single subcutaneous administration of test item RZL-012 at the doses of 5, 10, and 20 mg/kg in Sprague-Dawley rats resulted in non-systemic effects and or local effects at the treated skin area. Few changes observed in haematological parameters (WBC count, neutrophils, monocytes and eosinophils) were considered secondary effects due to inflammatory response (local skin reactions). The changes observed in clinical chemistry parameters (increased BUN in males and females and increased creatinine and AST levels in females) at all the doses tested and histopathological changes in kidneys (necrosis in tubular epithelium) at 20 mg/kg were considered systemic effects. Methods and results from the extended single dose toxicity study are described in the Investigator's Brochure.

Considering skin changes as non-systemic effects and or local effects, the NOAEL was determined at 10 mg/rat with an average body weight of 246.2 g for females and 255.2 g for male, under the test conditions and doses employed.

1.2.2.1.2. Pigs

This study was conducted to evaluate the potential local and systemic toxicity as well as efficacy of the test article, RZL-012 (50 mg/mL), in domestic Yorkshire crossbred swine following

subcutaneous injection into the subcutaneous abdominal fat on Day 0. Methods and results from the extended single dose toxicity in pigs study are described in details in the Investigator's Brochure.

Assessment of toxicity was based on mortality, clinical observations, body weight, qualitative food consumption, body temperature, subcutaneous fat temperature, blood pressure; physical and electrocardiographic examinations; and anatomic and clinical pathology. Blood samples were collected and analyzed for porcine stress syndrome testing, histamine level analysis, and toxicokinetic assessment of the test article.

Administration of the test article was not associated with any mortality, clinical observations (with the exception of transient redness and swelling at injection sites), body weight or food consumption changes, effects on electrocardiographic endpoints, or changes clinical chemistry or coagulation parameters. It should be noted that three animals died during the post anesthesia recovery period. The cause of death was considered to be related to perioperative complications associated with the anesthesia and not related to RZL-012 or saline administration. These three animals were replaced on study.

A slight elevation in body temperatures was noted in males treated with the test article from Days 14-16 until Days 77-79. In addition, several animals were observed with perioperative hyperthermia and/or hypothermia. To determine if the perioperative hyperthermia and/or hypothermia was caused by Porcine Stress Syndrome all remaining animals on study were tested and determined to be normal (negative).

Administration of the test article was associated with changes in subcutaneous fat temperatures, a mild increase in neutrophils, and macroscopic and microscopic observations.

A noticeable difference in subcutaneous fat temperatures was noted between treatment groups. Beginning as early as Day 4-5, an increase in temperature was noted at all test article treated sites in both males and females. The increase in temperature was noted through Days 58-63. At study termination, subcutaneous fat temperatures at treated sites were comparable to vehicle control.

Subcutaneous administration of RZL-012 (50 mg/mL) to farm pigs resulted in mild increases in neutrophils in both sexes at the 24 hour post-dose collection, which were most typical of an inflammatory response. Increases in neutrophils had resolved by the Day 14 collection.

Analysis of the plasma samples following subcutaneous administration of RZL-012 (Group 4) found that both female and male farm pigs were exposed to RZL-012. Mean systemic exposure (area under the concentration versus time curve between zero and the 24 hour timepoint [$AUC_{0\text{-}24hr}$]) and maximum observed concentration (C_{max}) values, were 3700 (hr*ng/mL) and 529 (ng/mL), respectively, for males and mean systemic exposure ($AUC_{0\text{-}24hr}$) and C_{max} values, were 2940 (hr*ng/mL) and 528 (ng/mL), respectively, for females.

Upon evaluation of the injection site photographs, no irritation was observed but transient redness was noted. Upon microscopic evaluation at 24 hours and 14 days, test article related findings in the injected subcutaneous tissue was noted. These findings were characterized by necrosis of the subcutaneous fat and muscle accompanied by acute inflammation at 24 hours post-dose. At 14 days, residual necrotic tissue in the injected areas was noted with evidence of on-going healing characterized by chronic inflammation and fibrosis. There was no evidence of systemic toxicity at 24 hours or 14 Days

The 14 day interim results of this study demonstrated that administration of 5.68 to 7.14 mg/kg to males and 5.32 to 6.33 mg/kg to females of RZL-012 (test article) over 20 injection sites in the pig was associated with expected changes in subcutaneous fat temperatures, transient changes in neutrophils, and marked localized irritation and tissue necrosis. The increase in subcutaneous fat temperature was considered to be related to the mechanism of action of RZL 012, and an indication of the efficacy of the test article. The microscopic changes noted at 24 hours were beginning to resolve at 14 days. The results of the final time point at 84 days will allow for assessment of the resolution of these findings.

Based upon the interim results of the study a NOAEL of 7.14 mg/kg in males and 6.33 mg/kg in females of RZL-012 has been established in the swine. The establishment of the NOAEL was based upon the microscopic effects being limited to the subcutaneous tissue with no systemic effects and the evidence of on-going healing at 14 days.

1.2.3. Additional Nonclinical Studies

- Secondary pharmacology (searching for off-target receptors).
- Establishing pharmacokinetic parameters and investigation of RZL-012 metabolism by liver enzymes and half maximal inhibitory concentration (IC_{50}) in cell-culture.
- Testing RZL-012 mutagenicity, utilizing the Ames test.
- Pyrogenicity in rabbits.
- Assessment of RZL-012 binding to the β3 receptor in cellular and nuclear receptor functional assays.
- Assessment of RZL-012 uptake by the 5-HT neurotransmitter in the absence and presence of a 5-HT2B agonist.
- Assessment RZL-012 effect on 5-HT neurotransmitter uptake and release in cellular and nuclear receptor functional assays.
- ADME-Toxicology
- Genotoxicity

Methods and results from these safety studies are described in the Investigator's Brochure.

1.2.4. Clinical Studies

Raziel Therapeutics has conducted an Exploratory phase 0, randomized, double-blind, vehicle-controlled study aimed at the evaluation of safety and thermogenesis-induction of three

escalating doses of RZL-012 drug product in overweight and obese volunteers. In each cohort, 8 subjects were enrolled, 6 active and 2 control. Study design is presented in the following table:

Table 1: Phase 0 Clinical Trial Design

	Cohort 1	Cohort 2	Cohort 3
Number of Subjects – Active/Placebo	6/2	6/2	6/2
Total Dose RZL-012 (mg)	5	10	20
Dose per NOAEL*	$1/50^{th}$	$1/25^{th}$	$1/12.5^{th}$
Number of Injections	1	2	4

Primary objective: Evaluation of the overall safety and preliminary efficacy of RZL-012 after subcutaneous injection and the existence of a thermogenic effect.

Secondary objective: Determination of RZL-012 pharmacodynamics and pharmacokinetics. Evaluation of the extent, duration and tissue associated changes of the thermogenic response to RZL-012, via minimal invasive means including injected-site thermogenesis imaging, Magnetic Resonance Imaging (MRI) and punch biopsy following injection into the subcutaneous fat.

Primary Endpoints:

Safety: The main objective was the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat. Therefore, the primary safety endpoint was the incidence of intolerable adverse events. The dose escalation scheme was stopped if at any dose cohort, 2 patients experienced intolerable side effects.

Efficacy: The primary efficacy endpoint was a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera. A thermogenic effect was defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the non-injected site, apparent at least 28 days after injection and non-related to inflammatory response as determined by inflammatory cytokines. The primary efficacy evaluation was supported by results from secondary endpoints, including MRI, biopsy and biomarkers.

Secondary Efficacy Endpoints:

1. Duration of the thermogenic effect, defined as a net-delta ≥ 1.

2. Local reduction in fat mass as determined by MRI.

3. Clinical laboratory changes from baseline, including improvement in fasting blood glucose and lipid profile.

4. Establishing pharmacokinetic profile for RZL-012.

5. Anthropometric changes from baseline, including body weight change.

6. Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site.

7. Change from baseline in inflammatory markers and cytokines.

Results:

This was a dose escalation exploratory clinical trial of RZL-012, a first-in-class, new chemical entity.

RZL-012 was generally found to be safe in all cohorts. There were no clinically significant changes in vital signs, ECG and almost all blood laboratory tests. Most AEs associated with RZL-012 injection occurred confined to the injection site and were transient. Biopsy from the injected site revealed no damage to the skin 56 days following RZL-012 injection. The only significant local AE was an abscess in one subject in the lower abdomen on the injected side, but at a considerable distance from the site of injection.

In another patient, a severe elevation of ALT blood levels and a moderate elevation of AST blood levels were seen 14 days following injection. This elevation was transient (resolved within 14 days). In light of the pre-clinical findings (increased AST blood levels in female rats sacrificed on Day 2 following RZL-012 injection) and in light of the findings in this clinical trial, Raziel therefore plans to monitor closely (on 24hr, Day 3, Day 7, Day 14, Day 21, Day 28 and will follow further if necessary) liver functions in the next clinical trial. There were no other systemic clinically significant AEs.

The exploration of thermogenesis induction by RZL-012 in humans was successful. A raise in temperature at the injection site was mostly evident in cohort 3 (the highest dose) at Day 14 or Day 21 following injection in RZL-012 treated subjects only. This change in temperature was captured and recorded by the infra-red camera.

Although not statistical significant, a drop in the change from baseline in Subcutaneous Fat Mass (SFM) ratio (treated/control) over time by MRI in RZL-012 treated subject of cohort 3 was evident in 5 of 6 treated subjects. The drop in subcutaneous fat associated with a drop in weight (more than 1 kg) and BMI when compared to baseline and is evident in 4 of 6 RZL-012 treated subjects of cohort 3 on Day 28 and/or Day 56, while controls gained weight and increased BMI.

Biopsy did not yield enough tissue (because punch biopsy did not penetrate deep enough to reach the remodeled tissue), and therefore, it was not possible to demonstrate that thermogenesis is due to adipose tissue remodeling by.

Although not statistical significant, a decrease in TC and FFA blood levels was evident in subjects of the RZL-012 treated group in cohort 3. This may imply to the mode of action of RZL-012 as stimulation of a thermogenic tissue such as BAT, is known to cause a systemic

effect via the mobilization of glucose and FFA from the blood stream to feed the ongoing local thermogenesis. Thus, lipolysis of WAT triacylglycerols (TAG) stores is accelerated and the uptake of FA derived from blood-born lipoproteins is increased due to the action of lipoprotein lipase (LPL). Raziel assumes that circulating FFA utilization by the RZL-012-induced thermogenic tissue resulted in lower levels of FFA in the blood, a process that may be beneficial for health. There was no consistent pattern to suggest a connection between inflammation markers and cytokines levels and changes in thermogenic activity reflecting the intended effect of the drug as opposed to local inflammation and distinguish between events related to M1 and M2 macrophages. Though, an increase in Adiponectin blood level was evident at Day 21 and Day 28 in 3 of 6 subjects treated with RZL-012, but not in controls. Adiponectin was found to be an obligatory mediator of cold-induced browning of WAT (8). Adiponectin can be elevated under various conditions, including those that trigger tissue remodeling in favor of thermogenesis such as chronic cold exposure. Although we do not know what triggered elevation of adiponectin in this study, it is known that downstream effects of adiponectin can promote the type of tissue remodeling we are expecting.

Raziel concludes that the potential risk-benefit balance for RZL-012 is favorable, and that it is likely that higher doses of RZL-012 will generate better results. This will be assessed in the next clinical trial

Methods and results of this exploratory study are described in the Investigator's Brochure.

2. PURPOSE AND STUDY OBJECTIVES

2.1. PURPOSE

This phase 2a clinical trial aims to test safety and efficacy of a new chemical entity, RZL-012, in converting WAT into a thermogenic tissue and reducing fat-mass in overweight and obese males.

2.2. STUDY OBJECTIVES

2.2.1. Primary

The primary objective is the evaluation of the overall safety and preliminary efficacy of RZL-012 after subcutaneous injection.

2.2.2. Secondary

The secondary objective is the determination of RZL-012 pharmacodynamics and pharmacokinetics. Evaluation of the existence of a thermogenic effect and the extent, duration and tissue associated changes of the thermogenic response to RZL-012, via minimal invasive means (injected-site thermogenesis, MRI and biopsy) after subcutaneous injection into fatty tissue below the skin.

3. STUDY DESIGN

3.1. DESCRIPTION OF STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, consecutive 4 cohort, dose escalation clinical trial that will enroll 8 subjects, 6 active and 2 control in all cohorts.

3.2. DOSE RATIONALE

The initial dose was determined by the NOAEL established by the GLP extended single dose toxicology study and by the previous phase 0 clinical trial in which 20mg RZL-012 was the highest dose achieved. This initial study is an escalating dose study. If no more than 1 subject experiences intolerable side effects within 14 days following the injection of the last dosed group, according to schedule, an additional cohort of volunteers will be administrated the next dose level.

Cohort 1: 40 mg RZL-012 (1/6.25th of the NOAEL determined in the GLP Toxicology studies).

Cohort 2: 80 mg RZL-012 (1/3.125th of the NOAEL determined in the GLP Toxicology studies).

Cohort 3: 120 mg RZL-012 (1/2.34375th of the NOAEL determined in the GLP Toxicology studies).

Cohort 4: 180 mg RZL-012 (approximately the NOAEL determined in the GLP Toxicology studies).

3.3. DOSING

3.3.1. Dosing Regimen

The dosing regimen will be a single dose treatment injection of RZL-012 in multiple sites.

The first 6 subjects randomly assigned to the RZL-012 treatment group (cohort 1) will initiate at the dose of 40 mg RZL-012 (approximately 1/6.25th the NOAEL as determined in the GLP toxicology study) and 2 more subjects will be given placebo (vehicle).

If no more than 1 subject experiences intolerable side effects within the 1st cohort, 14 days following the injection of the last dosed subject, an additional 6 subjects will receive a dose of 80 mg RZL-012 (approximately 1/3.125th of the NOAEL) and 2 more subjects will be given placebo (vehicle).

If no more than 1 subject experiences intolerable side effects within the 2nd cohort, 14 days following the injection of the last dosed subject, an additional 6 subjects will receive a dose of 120 mg RZL-012 (approximately1/2.34th of the NOAEL) and 2 more subjects will be given placebo (vehicle).

If no more than 1 subject experiences intolerable side effects within the 3rd cohort, 14 days following the injection of the last dosed subject, according to schedule an additional cohort of 6 volunteers, as above, will receive 180 mg RZL-012 (1/1.39 of the NOAEL). Additional 2 subjects in the cohort will serve as control and will be injected placebo (vehicle).

Dosing of the first 3 subjects in each cohort will progress consecutively from one individual to the other at 7-day intervals. For additional precaution, the first 3 subjects will be forced randomization with 2 active and 1 control. This study design will allow the physicians to monitor safety in a single subject at each dose; nevertheless, the blindness will remain intact.

The next subjects in the cohort will be randomized to either active treatment or placebo in a ratio determined by the number of subjects targeted for each cohort. Dosing of the next subjects will be in couples and the last subjects will be in a triplet.

If 1 subject had already experienced intolerable side effects in a cohort, then enrollment will progress consecutively from one individual to the other at 7-day intervals until that cohort is complete.

The trial will proceed within a cohort and from one cohort to the next as long as no more than one subject experiences intolerable side effects in the lower-dose cohort, and based on the decision made by a DSMB. The decision to proceed to the next cohort will be made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject in each cohort. The DSMB will be comprised of two independent medical doctors (MDs) expert in early phase clinical trials.

3.3.2. Intolerable Side Effect

Safety will be the principal primary endpoint of this study, as such if there are 2 intolerable and at least possibly related side effects observed in any dose cohort, that dose cohort will be stopped and only tolerable doses used for future subjects.

An intolerable side effect defined as any of the following treatment-related adverse drug reactions (ADRs):

- Any Grade 3 or greater event except for the following (For the following entities, a discussion will be held by the PI, DSMB and Sponsor to decide whether considered as an intolerable side effects):
    - Flu-like symptoms and fever that responds to standard treatment within72 hours
    - Localized edema and erythema
    - Pruritus
    - Pain
    - Skin/soft tissue inflammation
    - Fat Atrophy
    - Liver enzymes abnormality

- Non-significant lab abnormalities, lasting less than 7 days

To establish a threshold for clinical abnormalities and liver enzyme abnormalities the following tables were formed for main expected side effects. For the following abnormalities, intolerable side effect would be any Grade 3 or greater event:

Clinical Abnormalities Table

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity Repeated use of non-narcotic pain reliever > 24 hours	Interferes with activity	Any use of narcotic pain reliever beyond 7 days following injection or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Discomfort to touch or with movement	Significant discomfort at rest	Prevents daily activity	ER visit or hospitalization
Erythema/Redness *	2.5 - 7 cm	7.1 - 15 cm	> 15 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 - 7 cm and does not interfere with activity	7.1 - 15 cm or interferes with activity	> 15 cm or prevents daily activity	Necrosis

***** Erythema – the measured local reaction at the greatest single diameter beyond the injected area surface of all injections (4x8 cm for the first cohort, 8x8cm for the second cohort and 12x8cm for the third and fourth cohort), the measurement should be recorded as a continuous variable.

**Induration — the measured local reaction at the greatest single diameter beyond the injected area surface of all injections (4x8 cm for the first cohort, 8x8cm for the second cohort and 12x8cm for the third and fourth cohort), the measurement should be recorded as a continuous variable.

Liver Enzyme Abnormalities Table

Serum *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Liver Function Tests –ALT, AST increase by factor	3 x ULN	3 – 5 x ULN	5-10 x ULN beyond 10 days	> 10 x ULN beyond 10 days

Study discontinuation is to be considered by the investigator in any case of an intolerable side effect, and the actions taken are to be fully documented in source documents and Case Report Forms (CRFs).

To be considered an intolerable side effect, such an event must be considered to be possibly or probably related to the study drug.

Subjects experiencing an intolerable side effect will be withdrawn from the study, but followed for toxicity.

The study may also be prematurely terminated in any of the following cases:

- Recurring serious or severe ADR clinically evaluated by DSMB as warranting study termination.
- A decision made by Sponsor and/or IRB/EC and/or local regulatory agency to terminate the study.

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINTS

Safety: The main objective is the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat. Therefore, the primary endpoint will be the incidence of intolerable side effects and all adverse events of RZL-012 injection into the subcutaneous fat. The dose escalation scheme will be stopped if at any dose cohort, 2 patients will experience intolerable side effects.

Efficacy: The primary endpoint for efficacy is a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera. A thermogenic effect is defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the non-injected site, apparent at least 28 days after injection and non-related to inflammatory response as determined by inflammatory cytokines. The primary efficacy evaluation will be supported by results from secondary endpoints, including MRI, biopsy and biomarkers.

4.2. SECONDARY ENDPOINTS

Following are the study's secondary endpoints:

1. Duration of the thermogenic effect, defined as a net-delta ≥ 1, see definition in Section 6.1.17.2.1.
2. Local reduction in fat mass as determined by MRI, see definition in Section 6.1.17.2.2.
3. Clinical laboratory changes from baseline including improvement in fasting blood glucose and lipid profile, see definition in Section 6.1.17.2.3.
4. Establishing pharmacokinetic profile for RZL-012, see definition in Section 6.1.15.

5. Anthropometric changes from baseline, including body weight change, see definition in Section 6.1.17.2.4.
6. Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site, see definition in Section 6.1.17.2.5.
7. Change from baseline in inflammatory markers and cytokines, see definition in Section 6.1.17.2.6.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

Subjects meeting all of the following criteria will be eligible for study participation:

1. Adult male subjects 20-60 years old.
2. Subject is considered overweight and obese, with $27.5 < \text{Body Mass Index (BMI)} \leq 34.9$.
3. Significant subcutaneous abdominal fat as defined by $\text{WHR} \geq 0.9$.
4. Subjects with stable weight in the last 3 months by medical history.
5. Not one of the following eating disorders by subject's declaration: anorexia nervosa, bulimia nervosa.
6. Generally considered healthy according to medical history, physical examination, ECG and laboratory evaluation with a special emphasis on metabolic parameters (fasting glucose concentration < 100 mg, normal blood pressure).
7. Subject is willing to refrain from sexual activity or agrees to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012.
8. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study.
9. Subjects must sign an informed consent indicating that they are aware of the investigational nature of the study.

5.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded:

1. Subjects weighing less than 75 kg.
2. Subjects who have reduced/gained weight more than 5 % of their current body weight in the last 3 months.
3. Unable to tolerate subcutaneous injection.

4. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator put the subject at significant risk, are not eligible.
5. Subjects who test positive to Hepatitis B virus (HBV), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV) are not eligible.
6. Subjects with a clinical history of primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids are ineligible.
7. As a result of medical review, physical examination, the Principal Investigator (PI) (or medically qualified nominee) considers the subject unfit for the study.
8. Medication use on regular basis including blood and blood products.
9. Positive drug and alcohol tests.
10. Known sensitivity to components of the injection formulation.
11. Prior wound, tattoo or infection in the treated area.
12. Excessive growth of hair in the abdomen region.
13. Claustrophobia or MRI incompatible device or implant.

5.3. SUBJECT IDENTIFICATION

A unique code numbers will be assigned by the investigator to the trial subject rather than the subjects' names, personal identification numbers, and/or addresses to protect the subject's identity. The code numbers and initials will be used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

5.4. REMOVAL, REPLACEMENT OR EARLY WITHDRAWAL OF SUBJECTS FROM ASSESSMENT NOT DUE TO INTOLERABLE SIDE EFFECTS

In the first and second cohorts, if only one subject is withdrawn or removed from the study, and no more than one subject experience intolerable side effects, then the subject will not be replaced. If more than one subject is withdrawn or removed from the study, and more than one subject experience intolerable side effects, then the subject will be replaced by new subject.

In the third and fourth cohort, any withdrawal or removal not due to intolerable side effects within the first 28 days will be replaced by a new subject.

6. STUDY PROCEDURES AND ASSESSMENT

6.1. DEFINITIONS OF STUDY PROCEDURES

6.1.1. Informed Consent

Prior to initiation of any study procedures, each subject will undergo an Informed Consent process in which the subject voluntarily confirms their willingness to participate in the trial, after having been informed of all aspects of the trial relevant to their decision to participate. The investigator, or a person designated by the investigator, will fully inform the subject of all pertinent aspects of the trial. In addition, the investigator, or a person designated by the investigator, will inform the subject that he is free to refuse to enter the study or to withdraw from the study at any time, for any reason.

The Informed Consent Form (ICF) approved by the IRB/EC will contain a description of the study's purpose, procedures, inconveniences and potential risks, and anticipated benefits.

Prior to a subject's participation in the trial, an ICF will be signed and personally dated by the subject and initialed by the person who conducted the Informed Consent discussion.

If a subject is unable to read, an impartial witness should be present during the entire Informed Consent discussion. After the written Informed Consent form is read and explained to the subject and after the subject has orally consented to participating in the trial and, if capable of doing so, has signed and personally dated the Informed Consent form, the witness should sign and personally date the ICF. By signing the ICF, the witness attests that the information in the ICF was accurately explained to, and apparently understood by, the subject and that Informed Consent was freely given by the subject.

Prior to participation in the trial, the subject will receive a copy of the signed and dated written ICF. During participation in the trial, the subject will receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

The investigator should document in the source data that the Informed Consent was signed prior to subject's participation in the study and according to the ICH guidelines, as described above.

6.1.2. Medical History

Subjects' medical history should be fully documented at screening Day 1 (28 through 7days prior to baseline), to ensure compliance with study inclusion criteria and the absence of circumstance mentioned in the exclusion criteria. Medical history information must include, but not be limited to past and present medical conditions, concomitant non-drug treatments and hypersensitivity to drugs.

6.1.3. Concomitant Medication

All concomitant medication given 3 months prior to study entry, including blood and blood products dietary supplements, and non-prescription drugs will be listed at screening/baseline. Each entry will include the treatment's start date, treatment name (Generic), reason for use, dosing regimen (dose and frequency of use), route of administration, and stop date (if applicable). The clinical significance of the medication use will be decided by the investigator. Study subjects will be routinely questioned for changes in the administration of concomitant medication during the trial.

6.1.4. Physical Examination

The investigator (or medically qualified nominee) will conduct a complete physical examination at screening Day 1 (performed 28 through 7 days prior to baseline). Clinically significant abnormal findings except overweight and obesity should be discussed with the Sponsor.

Additional physical examination to assess subject's safety will be performed on study visit on Day 28.

6.1.5. Vital Signs and Measurements

Subjects' vital signs will be measured at screening Day1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria.

Vital signs measurements will include systolic and diastolic sitting position blood pressure, pulse rate, respiratory rate, and body oral temperature.

Additional vital signs measurements to assess subject's safety will be performed at baseline visit (Day 0) prior to drug injection, 2h ± 30min following drug injection, the following day (Day 1) after drug injection (24h ± 2h) and on study visits every 7 days thereafter, i.e., Day 7, Day 14 etc.

Additional pulse rate measurements to assess subject's safety will be performed at baseline visit (Day 0) prior to drug injection and 1h, 2h, 4h, 8h, 12h, 24h following injection in the opposite hand of blood sampling.

6.1.6. Anthropometric Measurements

Subjects' anthropometric measurements will be measured at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion and exclusion criteria. Anthropometric measurements will include height, weight, waist circumference and hip circumference. All anthropometric measurements will be measured in the morning following 10-12hr fast (overnight) and according to the Center for Disease Control (CDC) Anthropometry Procedures Manual of the National Health and Nutrition Examination Survey (NHANES) January 2007 edition (9).

Additional anthropometric measurements (apart from height) will be performed at Screening Day 2 before the MRI to ensure compliance with study inclusion and exclusion criteria, at -clinic admission visit (Day -1) and on study visit on Day 28. In subjects that are followed for over than 28 days, anthropometric measurements (apart from height) will be conducted on visit days attended at the study site every 28 days for a maximum period of additional 5 months. Additional weight measurements will be performed on weeks when weight is not measured at the site visits. In this case, weight will be measured by the subjects at their homes once a week in the morning following 8-12hr fast (overnight) and at bedtime. Subjects will be given a diary to record their weight.

6.1.6.1. Weight

Subjects' Weight will be measured in order ensure compliance with exclusion criteria and to calculate the BMI and ensure compliance with study inclusion criteria ($27.5 < BMI \leq 34.9$).

The subject will be instructed to stand completely still in the center of the scale platform with the feet close together hands at the sides and looking straight ahead. The weight measurement will be taken for the electronic readout and is recorded in kilograms to one digit after the decimal point.

6.1.6.2. Height

Subjects' Height will be measured in order to calculate the BMI and ensure compliance with study inclusion criteria ($27.5 < BMI \leq 34.9$).

The standing height or stature measurement is an assessment of maximal vertical size. This measure is for persons who are able to stand unassisted. Standing height is measured with a fixed stadiometer with a vertical backboard, a fixed floorboard, and movable headboard. Hair ornaments, jewelry, buns, braids and cornrows should be moved or removed from the top of the head in order to measure stature properly. The subject will be instructed to stand on the floorboard with the heels of both feet together, touching the base of the vertical board. The toes are pointed slightly outward at approximately a 60 ° angle. Body weight is evenly distributed with both feet flat on the floor. The technician will check the position of several points of body contact with the vertical board. The first contact point is the heels, followed by the buttocks, the scapula or shoulder blades, and finally the back of the head. Depending on the overall body conformation of the individual, all points may not touch. In such case, the trunk of the body should be positioned vertically above the waist with the arms and shoulders relaxed. The head should be aligned in the Frankfort horizontal plane. The head is in the Frankfort Plane when the horizontal line from the ear canal to the lower border orbit of the eye is parallel to the floor and perpendicular to the vertical backboard. Many people will assume this position naturally, but for some it may be necessary to make a minor adjustment. If required the technician may gently tilt the head up or down until proper alignment is achieved with the eyes looking straight ahead. Once correctly positioned the headboard is lowered. The subject is instructed to take a deep

breath and stand as tall as possible. A deep breath allows the spine to straighten yielding a more consistent and reproducible stature measurement. The headboard is positioned firmly on top of the head with sufficient pressure to compress the hair. The measurement will be read in centimeter and recorded in meters.

6.1.6.3. BMI

Subjects' BMI will be calculated in order to ensure compliance with study inclusion criteria ($27.5 < BMI \leq 34.9$) by the equation below:

BMI = weight (in kilograms)/ $(height)^2$ (in meters)

BMI will be computed to one digit after the decimal point

6.1.6.4. Waist Circumference

Subjects' Waist Circumference will be measured in order calculate the WHR to ensure compliance with study inclusion criteria ($WHR \geq 0.9$).

The subject will be instructed to gather his gown shirt above the waist, cross the arms, and place the hands on opposite shoulders. If necessary, lower the pants and underclothing to slightly below the waist. The technician will stand on the subject's right side and will palpate the hip area to locate the right ilium of the pelvis. With a cosmetic pencil, draw a horizontal line just above the uppermost lateral border of the right ilium. Cross this mark at the midaxillary line which extends from the armpit down the side of the torso. If it is difficult to find the iliac crest, such as on subjects with larger waists, then begin inferior to the midaxillary line (toward the subject front) and palpate the ilium upward to the midaxillary line until the uppermost part of the bone is found. Extend the measuring tape around the waist. Position the tape in a horizontal plane at the level of the measurement mark. Check that the tape sits parallel to the floor and lies snug but does not compress the skin. Always position the zero end of the tape below the section containing the measurement value. Take the measurement in centimeters to the nearest 0.1 cm at the end of the subject normal expiration (one digit after the decimal point).

6.1.6.5. Hip Circumference

Subjects' Hip Circumference will be measured in order calculate the WHR to ensure compliance with study inclusion criteria ($WHR \geq 0.9$).

The subject will be instructed to stand upright with feet together and weight evenly distributed. The buttocks or hip circumference is the only measure that is not taken directly on the skin. The assistant technician stands in front of the subject and gathers the fabric of the pants. The thumbs and index fingers hold the folded sides of the pants snugly. This minimizes the amount of material included in the measurement and helps to define the maximum protuberance of the buttocks when viewed in profile. The technician is positioned on the right side with eye level at

the hip region of the subject. The measuring tape is place around the hips and anchored at the maximum protuberance of the buttocks. The assistant then releases the folds of the pants and helps to adjust the tape so it is in a horizontal plane. The measuring tape is held snugly, but not pulled tight. The measure is recorded in centimeters to the nearest 0.1 cm (one digit after the decimal point).

6.1.6.6. Waist to Hip Ratio (WHR)

Waist to Hip Ratio (WHR) will be calculated in order to ensure compliance with study inclusion criteria (WHR $\geq$ 0.9) by the equation below:

WHR = Waist Circumference (in centimeters) / Hip circumference (in centimeters)

The WHR will be computed to two digits after the decimal point.

6.1.7. Serology Assays

Assays for Hepatitis C virus (HCV), Hepatitis B virus (HBV) and Human immunodeficiency virus (HIV) will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria.

6.1.8. Clinical Laboratory Tests

Clinical laboratory tests will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion and exclusion criteria. Additional studies will be conducted on different study visits according to schedule as written below. Clinical laboratory tests performed on Clinic Admission visit are performed in order to establish a baseline except from the following tests that are performed to confirm eligibility: urine drug screen and clinical significant results that the PI feels will risk the subject.

The maximum total blood volume will be 30 -100 mL per visit. Every out-of-range value will be assessed by a physician and deemed as either clinically significant (CS) or clinically not significant (CNS). Values that represent a change from baseline in subject's medical status according to the laboratory normal ranges will be adequately documented as an adverse event (AE) as described in Section 9.

6.1.8.1. Hematology

Hematology tests will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria. Additional Hematology testing will be conducted to assess subject's safety on -clinic admission visit (Day -1), at 24hr ± 2h following injection and on study visit Day -1, 1, 3, 7, 14 and 28.

Hematology tests will include Complete blood count (CBC) (including White blood cells [WBC] differential values) and coagulation tests: White blood cells (WBC), Red blood cells (RBC),

Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW), Platelets, Mean platelet volume (MPV), Fibrinogen, D-dimer, International normalized ratio (INR), Partial thromboplastin time (PTT) and Prothrombin time (PT).

6.1.8.2. Serum Chemistry Analysis

Testing of blood chemistry values will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria. At screening Day 1, subjects should be notified to come fasting (10-12 hours of fast) for fasting glucose, blood test.

Additional fasting glucose, insulin, leptin, lipid profile blood tests will be conducted at clinic admission visit (Day -1) and on study visit Day 28 and every 28 days during follow-up period.

Additional Serum Chemistry testing will be conducted at clinic admission visit (Day -1) to establish baseline values, 24hr ± 2hr following injection and on study visit Day -1, 1, 3, 7, 14 and 28.

Serum chemistry will include: Sodium, Calcium, Potassium, Phosphorus, Glucose, Liver enzymes (Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], Lactate dehydrogenase [LDH], Creatine-kinase MM [CK-MM], Gamma-glutamyltransferase [GTTP], Alkaline phosphatase [ALP]), Bilirubin, Creatinine, Urea/Blood urea nitrogen [BUN], Total protein, Albumin, Amylase, Creatine phosphokinase [CPK]

Lipid profile will include: (Triglycerides [TG], High-density lipoprotein [HDL], Low-density lipoprotein [LDL], Total-cholesterol [TC] and Free-fatty-acids [FFA]).

In case of CK-MM >x5 ULN, subjects will undergo clinical assessment for symptoms and alternative causes, and renal function will be assessed (including urinalysis).

6.1.8.3. Urine Drug Screen

Urine drug screen will be conducted at screening Day 1 and at clinic admission visit (Day -1) in order to ensure compliance with study exclusion criteria.

Drugs of abuse will include: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, alcohol, opiates, phencyclidine and propoxyphene.

6.1.8.4. Inflammatory Markers and Cytokines

Testing of inflammatory markers and cytokines values from the 2nd, 3rd and 4th cohorts (on RZL-012 treated and placebo treated subjects in each cohort) will be conducted in order to explore the mode of action at clinic admission visit (Day -1)to establish baseline values (4 mL

blood per subject). Additional cytokines testing will be conducted study visits Day 7, 14, 21 and 28.

Inflammatory and cytokines will include: CRP, Adiponectin, CD-163, Interleukin [IL]-1β, IL-4, IL-6, IL-10, IL12p70, IL-13, IL-23, Tumor necrosis factor [TNF] α, and TGFβ1.

Inflammatory and cytokines level will be measured by multiplexed ELISA kits, called Q-Plex™. Q-Plex Arrays are able to measure the concentration of multiple proteins in each sample and to quantify cytokines levels. Blood samples (4 mL) will be centrifuged at 1200 G in 4 ^{0}C for 10 minutes, plasma collected in aliquots (minimum of 2 aliquots of 500 µL each) within 20 minutes of centrifugation and flash frozen on dry ice. Processed samples will be frozen in -80 ^{0}C. Plasma aliquots will be analyzed by Quansys Biosciences.

6.1.8.5. Histamine

Testing of subjects' blood histamine levels will be conducted at clinic admission visit (Day -1) visit before drug injection in order to establish a baseline (4 mL blood per subject). Additional blood histamine levels will be conducted the day following drug injection (24h ± 2h following drug injection), at study visit Day 3 and 14.

6.1.8.6. Urinalysis

Urinalysis will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria and to allow differential diagnosis in case of urinary tract associated AE. Additional urinalysis testing will be conducted on study visit Day 14 and 28.

Urinalysis will include: Nitrite, Sodium, Potassium, Calcium, Phosphate, Protein, RBC, WBC, Blood, Glucose, Ketone bodies, Bilirubin, Urobilirubin, Urine specific gravity, Osmolarity, and pH.

6.1.9. ECG

Subjects' ECG will be performed at screening Day 1 (performed 28 through 7 days prior to baseline) in order to ensure compliance with study inclusion criteria. ECG is to be performed on at least a triplicate of heartbeats for all measurements and will be recorded at a speed of 25 mm/sec. Additional ECGs will be performed at 4h ± 30min, 12h ± 30min and 24h ± 2h following drug injection (Day 0-1) and on Days 14 and 28.

Computerized ECG analysis will include: Heart rate, Rhythm, PR interval, QRS axis, and QRS duration. QT interval and QTc will be calculated manually according to the Bazett formula. ECG will be recorded at a standard speed of 25 mm/sec and standard amplitude of 10 mm/mV.

6.1.10. Draize Score

Subjects' skin irritancy will be evaluated by Draize score at screening Day 1 (performed 28 through 7 days prior to baseline) in order to establish a baseline to compare following drug injection.

Additional skin irritancy evaluation to assess subject's safety will be performed at baseline visit prior to injection, and on 2h ± 30min following injection, on the following day 24h ± 2h after drug injection and on study visits Day 7, 14, 21, and 28. For the 1st and 2nd cohorts if by visit Day 56 Draize score is not 0 for erythema and edema, then subject will continue to be followed every 28 days till Draize score is 0. If Draize score is 0 for erythema and edema, then subjects of these cohorts will be followed for additional 2 months (every 28 days) by phone for adverse events. For the 3rd and 4th cohorts (or the highest dose achieved) Draize score will be assessed every 28 days during the follow-up period.

Skin irritancy observations in the injected sites and contra-lateral sites will be scored using the Draize scale for scoring skin reaction:

Erythema and eschar formation		**Edema formation**	
No erythema	0	No edema	0
Very slight erythema (barely perceptible)	1	Very slight edema (barely perceptible)	1
Well defined erythema	2	Slight edema (edges are well defined by definite raising)	2
Moderate to severe erythema	3	Moderate edema (raised approximately 1mm)	3
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4	Severe edema (raised more than 1mm extending beyond area of exposure)	4

- Total possible erythema score = 4
- Total possible edema score = 4

6.1.11. Photography of the Injected Site

Documentation of the skin condition and fat reduction effect in the injected area compared to the contra-lateral non-injected area will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline). Additional photography will be performed at Day 1 (24h ± 2h following drug injection) and on study visits Day 7, 14, 21, and 28. In subjects that are followed for over 28 days, photographing will be conducted every 28 days.

Photography with a digital camera will include:

1. The injected area - at a distance of 20 cm and in a horizontal line from the umbilicus.
2. The contra-lateral non-injected area - at a distance of 20 cm and in a horizontal line from the umbilicus.

3. The injected area and the contra-lateral non-injected area – at a distance of 1 m and in a horizontal line from the umbilicus.
4. The injected area - at 45 degree angle from the camera and in a horizontal line from the umbilicus
5. The contra-lateral non-injected area – at 45 degree angle from the camera and in a horizontal line from the umbilicus.
6. The injected area - oblique views.
7. The contra-lateral non-injected area - oblique views.

Photography with a digital camera will be performed according to a detailed written manual.

6.1.12. Thermal Imaging

Evaluation of the thermal effect in the injected area compared to the contra-lateral non-injected area will be conducted at screening Day 1 (performed 28 through 7 days prior to baseline). Additional thermal imaging will be performed at clinic admission visit (Day -1), the day following drug injection (24h ± 2h following drug injection) and on study visits Day 7, 14, 21, 28, and 56.

For the 3rd and 4th cohort (or in the 2nd cohort if 2 subjects experience intolerable side effects in the 3rd cohort) additional thermal imaging will be conducted every 28 days for an additional maximum period of 5 months.

Thermal imaging is non-invasive, non-radiating device that passively measures the emitting infra-red radiation of body surface with a sensitive (± 0.1 °C) Infra-Red thermal camera (FLIR A310, ISO 9001-2008 Certified). Thermal imaging will include: a view of the injected area and the contra-lateral non-injected area – at a distance of 1 meter and in a horizontal line from the umbilicus. Thermal imaging will be performed in a room of 25 ± 1 °C to reduce environmental influences on temperature reading according to a detailed written manual.

6.1.13. Fat Tissue Imaging: Magnetic Resonance Imaging (MRI)

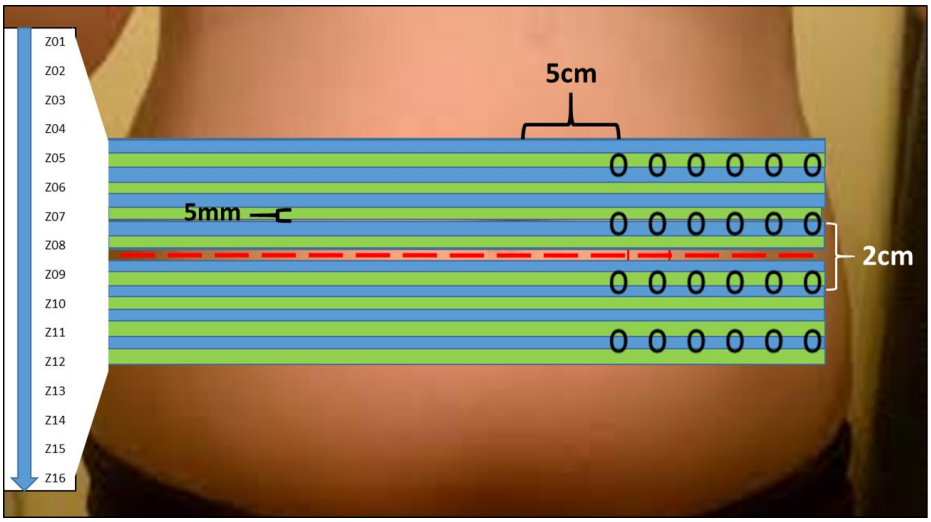
Evaluation of Magnetic Resonance Imaging (MRI) in all cohorts will be conducted in eligible subjects after 2-hour fast at screening Day 2 (performed 14 through 2 days prior to baseline) and on Day 28.

For the 2nd cohort an additional MRI scan will be performed on Day 56.

For the 3rd and 4th cohort (and for the 2nd cohort if subjects experience intolerable side effects in the 3rd cohort) additional MRI scans will be performed every 28 days for an additional maximum period of 5 months

MRI scans of the abdomen will be performed using a 1.5 Tesla machine (General Electric - Signa or Siemens) using a body coil. Subjects will be examined after 2-hour fast in the supine position with arms positioned parallel along the lateral sides of the body. A breath-hold technique will be used to avoid motion artifacts when chest and abdomen are scanned. MRI scans demonstrating fat in the different compartments will be assessed using a MATLAB-based program. Fat tissues of specific anatomical landmarks will be quantified. In order to calculate the fat mass, 16 consecutive slices of 5mm width will be used: eight above the umbilicus and eight under the umbilicus (Figure 1). The scanner will utilize a 3D modified DIXON (mDIXON) imaging technique without gaps (5mm thickness and spacing of 5mm), fast-low-angle shot (FLASH) sequence with a multi-echo two-excitation pulse sequence for phase-sensitive encoding of fat and water signals (TR,3.6ms; TE1,1.19ms; TE2,2.3ms; FOV 520×440×80mm; 2×1.4×1mm voxel size). Sixteen images of the phantoms will be generated, including in-phase, out-phase, fat and water phase. Images should be saved in a DICOM format with the information of date, subject's screening number and orientation (Left/Right) to be transferred by the Sponsor's request for analysis. MRI will be performed according to a detailed written manual.

Figure 1: MRI: Distribution of 16 Consecutive Slices

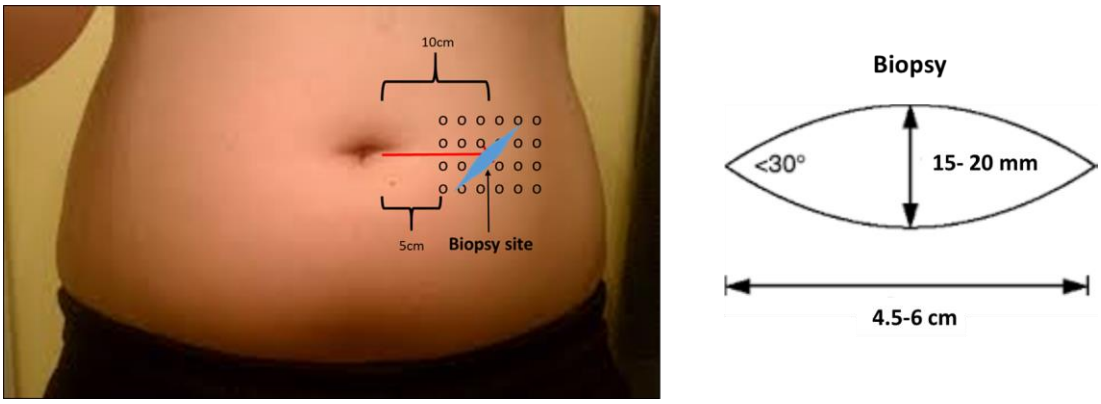


6.1.14. Biopsy

On Day 56 (following MRI), in 3 randomly selected subjects of the 3rd cohort (or the 2nd if 2 subjects experience intolerable side effects in the 3rd cohort) an abdominal SC adipose tissue biopsy will be taken from the injected side. The Sponsor or designee will select 3 subjects to go under a biopsy: two subjects who will be demonstrating clear thermogenesis (assuming an active) and one subject who will not demonstrate thermogenesis (assuming a control). Before biopsy the Sponsor representative who is un-blinded to the study will confirm that the selected subjects are indeed 2 RZL-012 treated and 1 vehicle treated. Subjects will be followed 7 days post biopsy and will terminate their study participation.

After local anesthesia, an elliptical excision biopsy will be conducted by a trained medical professional 10 cm lateral to the umbilicus lateral wall (Figure 2). A sample of fat tissue (a biopsy of an ellipse of 15-20 mm deep and 4.5-6 cm long, Figure 2) will be taken from the incision. For optimal cosmetic results the incision will be made on a slant following Langer's lines. The incision will be stitched appropriately and the wound will be covered with a bandage or sterile dressing. The sample will be divided in two. One half will be placed in a vial filled with a fixation solution (formaldehyde). After 24h ± 2h, the fixation solution should be exchanged to ethanol 80% and further processed for histological analysis. Each vial and lid will be labeled with: subject's name, subject's identification number and biopsy site. The other half of the biopsy will be embedded in a labeled cryomold with Optimum Cutting Temperature (OCT) compound and flesh frozen using a cryostat or liquid nitrogen. Each sample will be labeled with: subject's name, subject's identification number and biopsy site. Biopsies will be sent to the sponsor in an adequate manner and evaluated by a certified pathologist. Biopsies will be stained for hematoxylin and eosin stain (H&E) and further evaluated for BAT and other markers and morphometry.

Figure 2: Biopsy Site and Dimensions



6.1.15. Pharmacokinetics

Testing of RZL-012 Pharmacokinetics will be conducted at the baseline visit till the following day (Day 0-1). Subjects will stay overnight in the study center. Blood samples (10 mL blood per sample in K_2EDTA vials, 100 mL/subject/24h) will be taken after injection at the given time points: 0, 30, 60 min, 2h, 3h, 4h, 6h, 8h, 12h, 16h,24h, 30h in subjects from all cohorts. Whole blood samples (10 mL x12 time points) will be stored on an ice block or wet ice until centrifuged. Samples will be placed in the centrifuge and spin cycle started within 60 minutes of collection. Samples will be centrifuged at 1200 g in 4 °C for 10 minutes. Plasma will be removed and placed in aliquots (4 aliquots of 1 mL each) within 20 minutes of centrifugation and flash frozen on dry ice. Processed samples will be placed in frozen (-60 to -90 °C) storage. Determination of RZL-012 in K_2EDTA human plasma a validated method of Liquid Chromatography-Tandem Mass Spectrometry will be conducted and analyzed by Analyst Research Laboratories Ltd. Samples (2 aliquots/subject/time point) will be sent to Analyst frozen on dry ice and 2 aliquots will be retained for possible future analysis.

6.1.16. Adverse Events

The information obtained during weekly subjects questioning, review of subject's compliance record, physical examinations, vital signs measurements, blood testing, and by any other means will be evaluated in light of baseline medical data and thus provide the basis for adverse events identification and grading.

The trial will proceed within a cohort and from one cohort to the next as long as no more than one subject experiences intolerable side effects and based on the decision made by a DSMB. Proceeding from one cohort to the next will be based on the decision made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject in each cohort. The DSMB will be comprised of two independent MDs expert in early phase clinical trials.

The adverse events reported during the trial will be graded (see Section 9), documented, and assessed in light of their clinical significance and relation to investigational product. In addition, the following information regarding the AE must be obtained: AE description, start date, end date (if applicable) or ongoing, severity, seriousness, relationship to study drug, outcome (e.g., resolved / unresolved), and action taken (e.g., concomitant medication). The sponsor or the sponsor representative will provide information regarding SAE expectedness based on data included in the IB. Adverse event monitoring will be conducted throughout subject's participation up to 28 days after injection. For the 1st and 2nd cohort subjects will be additionally followed for AE at visit Day 56. If Draize score is 0 for erythema and edema, subjects of these cohorts and subjects of the 3rd and 4ths who terminate the study before visit Day 112, will be followed at Day 84 and Day 112 by phone-call questioning. For the 3rd and 4th cohort (or the highest dose achieved) adverse events will be recorded after Day 28 every 28 days if subject did not terminate participation in the study.

6.1.17. Evaluation of Response

Evaluation of response will be conducted on Day 7 and every 7 days thereafter till Day 28.

6.1.17.1. Evaluation of Primary Endpoints

6.1.17.1.1. Safety and Tolerability Monitoring

For determination of the study's primary end point, evaluation of safety and tolerability will be conducted according to definitions and guidelines below.

Safety and tolerability will be assessed by the study medical staff (e.g., PI, site coordinator, and study nurse) and the study subjects on the basis of the following:

1. AEs and Serious Adverse Events (SAEs), including severity, relation to study treatment and classification by whether or not these events comprise intolerable side effects.
2. Physical exams, Draize score and vital signs measurements.

3. Urine testing.
4. Blood laboratory testing for changes in hematology and chemistry values.
5. ECG
6. Subjects questioning - full medical history during screening, routine AE reporting and tolerability monitoring through review of subject's weight diary.

6.1.17.1.2. Efficacy Endpoint – Significant Thermogenesis

The study primary efficacy endpoint, a significant thermogenesis at the injected site will be evaluated by comparing with the contra-lateral, non-injected site. A significant thermogenic effect is defined as the increase of 1 °C from baseline in the difference in temperature (in °C) between the treated and not-treated sites (net delta). This thermogenesis should be apparent by 28 days after injection. The sites temperatures will be measured with a sensitive (± 0.1 °C) Infra-Red thermal camera.

6.1.17.2. Evaluation of Secondary Endpoints

6.1.17.2.1. Sustained Thermogenic Effect

Sustained thermogenic effect will be evaluated by thermal imaging. A sustained thermogenic effect is defined as an evident thermogenic effect after 28 days. A significant thermogenic effect is defined as the increase of 1 °C from baseline in the difference in temperature (in °C) between the treated and not-treated sites (net delta). The duration of the thermogenic effect will be evaluated in the lower dose groups till Day 56 and in the higher dose groups by thermal imaging every 28 days in those subjects demonstrating clear thermogenesis by 28 days after injection for a maximum period of an additional 5 months.

6.1.17.2.2. Local Fat Mass Reduction

Local reduction in fat mass will be evaluated by MRI. A local fat reduction is defined as a significant reduction (compared to baseline) in the average width of abdominal subcutaneous fat in the injected area compared to the contra-lateral area, SFM ratio, as evaluated by MRI. Local fat reduction in cohort 4 will be defined as a significant reduction (compared to baseline) in the average width of abdominal subcutaneous fat in the injected area compared to the surroundings area, SFM ratio, as evaluated by MRI. MRI will be evaluated in all groups at baseline and at Day 28. MRI will be evaluated in the cohort 3 (or in cohort 2 if 2 subjects will experience intolerable side effects within the 3rd cohort) and cohort 4 every 28 days for up to 6 months from the beginning of treatment.

6.1.17.2.3. Clinical Laboratory Changes

Clinical Laboratory Changes will be evaluated comparing to baseline. Clinical laboratory changes definition is a significant change from baseline according to the laboratory normal

ranges that affect the subject's medical status as assessed by the investigating physician, including improvement in fasting glucose and lipid profile.

6.1.17.2.4. Anthropometric Measurements Change

Anthropometric measurements will be evaluated comparing to baseline. Anthropometric measurements changes are defined as significant reduction in body weight, BMI and WHR at the end of the study compared to baseline.

6.1.17.2.5. Histological Changes

Histological changes will be evaluated comparing to known historical data. Histological changes definition is an evident change from known historical data of normal subcutaneous adipose tissue as assessed by an expert pathologist.

6.1.17.2.6. Inflammatory Markers and Cytokines Changes

To determine drug mechanism of action, inflammatory markers and cytokines level in cohorts 2 through 4 will be evaluated by comparing to baseline. Inflammatory markers and cytokines changes definition is an apparent change from baseline.

6.1.17.3. Compliance Monitoring

Compliance monitoring will include the following procedures:

- Compliance assessment by site coordinator at the study visit, including but not limited to subject questioning and review of the weight diary completed by the subject.
- Completion of weight diary by the subject.

6.1.17.4. Dispensing of RZL-012 Investigational Product

The RZL-012 investigational product will be dispensed to the study site under monitored conditions by Nextar Ltd. All procedures connected to investigational product's allocation (kits received at site, returned kits) will be properly documented, dated and signed in a designated site folder to allow full product tracking. Source documents will be kept for the duration required by local regulations and ICH-GCP (whichever is longer).

6.1.17.5. Questioning of Study Subjects

Questioning of study subjects during site visits and any unscheduled conversations (e.g., by phone) with site staff will be fully documented in subject file. Whenever possible, subject questioning should include, but not be limited to, inquiring information regarding occurrence and severity of AEs, treatment tolerability and compliance to future scheduled procedures and visits.

6.2. STUDY VISITS

Study visits will be fully documented in the CRF as described in Section 11. Documentation will be completed in a timely manner and within 5 working days to ensure protocol adherence and compliance with ICH-GCP.

6.2.1. Screening Procedures

All information collected and documented during screening procedures will be reviewed to ensure eligibility in reference to study inclusion and exclusion criteria, and fully documented in subject file.

Screening visit Day 1 should be performed no later than 7 days prior to baseline visit for all cohorts.

Subjects should be notified to come fasting (10-12 hours of fast) for the fasting glucose test and weight measurement. Subjects screening visit Day 2 should be performed no later than 2 days prior to baseline visit. Subjects who are alternates, and not dosed, the screening visit Day 2 should be performed no later than 12-14 days prior to baseline.

Study screening Day 1 procedures will include the following:

- Informed Consent - Section 6.1.1
- Medical History - Section 6.1.2
- Concomitant Medication - Section 6.1.3
- Physical Examination - Section 6.1.4
- Vital Signs and Measurements - Section 6.1.5
- Anthropometric Measurements - Section 6.1.6
- Serology Assays – Section 6.1.7
- Clinical Laboratory Tests - Section 6.1.8
- ECG - Section 6.1.9
- Draize Score – Section 6.1.10
- Photography of Injected Site – Section 6.1.11
- Thermal Imaging- Section 6.1.12
- Fasting glucose

Subjects may be rescreened if they were screened and not dosed within 14 days. The following procedures will be performed: Clinical Laboratory Tests (hematology, serum chemistry, and

urinalysis), vital signs, weight, BMI, waist and hip circumference WHR, Draize score, photography and thermal imaging.

Study screening day 2 procedure will include the following:

- Anthropometric Measurements - Section 6.1.6
- Fat Tissue Imaging: Magnetic Resonance Imaging (MRI) - Section 6.1.13

6.2.2. Study Randomization

Subjects will be randomized to each study group, i.e., investigational therapy or control, left side injection or right side injection according to a predefined randomization scheme. The investigational therapy group will be treated with RZL-012 and the control group will be treated with the same formulation (vehicle) as with RZL-012, absent active medication.

Masking will be used to blind the Investigator regarding randomization, i.e., assignment to study group will be disclosed only after subject eligibility is confirmed and immediately before treatment initiation. The pharmacist will be unmasked and will be responsible to fill the syringes for injection.

6.2.3. Study Treatment

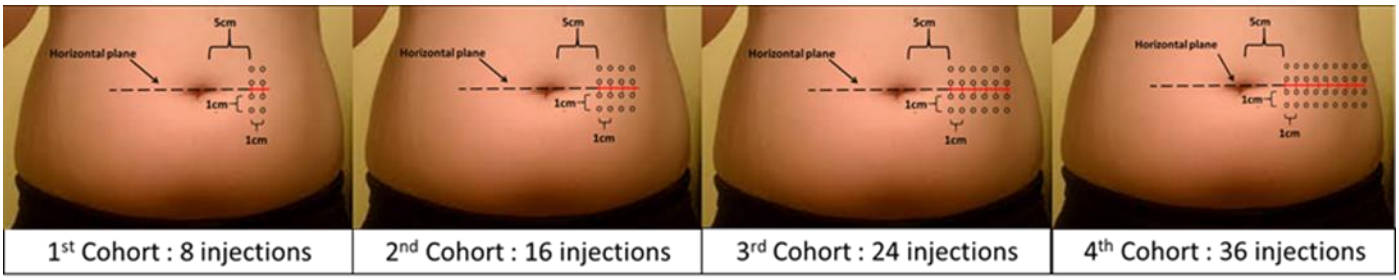
6.2.3.1. Treatment with RZL-012 Investigational Therapy

RZL-012 is an investigational product supplied as a single dose single treatment injection in multiple sites (8-48) of injections. Before injection, subjects will be advised to keep their regular diet and physical activity.

The injection dosing regimen and technique is crucial for the therapy safety and efficacy. Syringes will be filled by the pharmacist with 0.1 mL RZL-012 or vehicle and the number of syringes will be compatible with the number of injections. All injections will be administered diagonally in 45 °, using a 1 mL Luer-lock syringe and a 30 G x 1/2" needle.

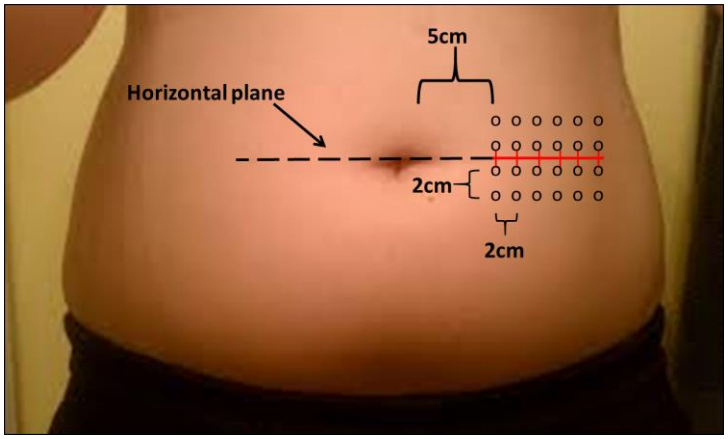
The injection will be administrated randomly into the left or right abdominal subcutaneous fat according to the randomization scheme (the hole of the needle pointing into the fat layer). A grid line will be drawn with a makeup pencil in a horizontal plane 5 cm lateral to the umbilicus lateral wall so that it will cut the injected points symmetrically (Figure 3).

Figure 3: RZL-012 Injection Sites



For the 1st, 2nd and 3rd cohorts one to four (depends on the number of injection sites) tick marks 2 cm apart will be drawn on the grid line. For the 4th cohort nine tick marks 1 cm apart will be drawn on the grid line. Thus, the distance between injected points will be 2 cm for the first 3 cohorts and 1 cm for the 4th cohort (Figure 4). The injection sites will be drawn with a makeup pencil. The needle will be inserted into the skin just above the pencil mark in a vertical manner towards earth. The hole of the needle should be pointing into the fat layer. An attempt to pull the plunger should be made before injecting to ensure that no blood is coming out. If so, the plunger should be pushed down to inject the medicine. The formulation is viscose; therefore, resistance is expected while injecting.

Figure 4: Design of the 24 Injection Sites



This study will be performed in a dose escalation manner:

Cohort 1: The first 8 subjects randomly assigned to the study group will receive either RZL-012 (6 subjects) or placebo (2 subjects). The initial dose of 40 mg RZL-012 (1/6.25th the NOAEL) is based on HED from GLP toxicology study and safety results of the highest dose cohort (20mg RZL-012) from phase 0 clinical trial. Subjects will receive 8 injections (0.1 mL in a 2x4 rows cluster) of 5 mg RZL-012. If no more than 1 subject experiences intolerable side effects within 14-days following the injection of the last dosed subject, according to schedule and following the DSMB approval an additional cohort will enter the study.

Cohort 2: The next 8 subjects randomly assigned to the study group will receive either RZL-012 (6 subjects) or placebo (2 subjects). The dose of 80 mg RZL-012 (1/3.125th the NOAEL) is based on HED from GLP toxicology study and safety results of cohort 1. Subjects will receive 16 injections (0.1 mL each in a 4x4 rows cluster) adding up to 10 mg. If no more than 1 subject experiences intolerable side effects within 14-days following the injection of the last dosed subject, according to schedule and following the DSMB approval an additional cohort will enter the study.

Cohort 3: The next 8 subjects randomly assigned to the study will receive either RZL-012 (6 subjects) or placebo (2 subjects). The dose of 120 mg RZL-012 (1/2.34th the NOAEL) is based on HED from GLP toxicology study and safety results of cohort 2. Subjects will receive 24 injections (0.1 mL each in a 6x4 rows cluster) adding up to 20 mg.

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If no more than 1 subject experiences intolerable side effects within 14-days following the injection of the last dosed subject, according to schedule and following the DSMB approval an additional cohort will enter the study.

Cohort 4: The next 8 subjects randomly assigned to the study will receive either RZL-012 (6 subjects) or placebo (2 subjects). The dose of 180 mg RZL-012 (1/1.39 the NOAEL) is based on HED from GLP toxicology study and safety results of cohort 3. Subjects will receive 36 injections (0.1 mL each in 9x4 rows cluster) adding up to 180 mg.

The decision to proceed to the next cohort will be made by DSMB after reviewing all safety data collected by Day 14 within 2 ± 1d.

Each RZL-012 kit contains 1 vial (250 mg/4.8 mL) corresponding to the number of subjects receiving treatment in each cohort.

RZL-012 will be injected on baseline study visit.

6.2.3.2. Treatment with Placebo

Two subjects randomly assigned to the study in every cohort group will be injected placebo, which will be a vehicle control (tween-80, propylene glycol, benzyl alcohol and water) in the same manner as mentioned above (Section 6.2.3.1).

6.2.4. Baseline Visit

Baseline visit is defined in the study as Day 0. Baseline visit will be performed to complete screening evaluation, and to review all procedures necessary to confirm subject eligibility. Subjects will stay overnight in the study center till 30h + 3h following drug injection.

Screening information may be considered for baseline data if acquired within the adequate timeframe as described in Table 2.

Table 2: Subject Information and Timeframes

Information	Timeframe	Follow-up Timeframe
Informed Consent Form	Signed prior to any study dedicated procedure	
Medical History and Concomitant Medications	At screening visit and at clinic admission visit (Day -1)	
Physical examination	At screening Day1 visit and at Day 28	
Vital Signs	At screening Day 1 visit and at Days 0 (pre and following injection), 1, 7, 14, 21, 28	
Pulse rate	At Day 0 (pre and following injection) and at day 1	
ECG	At screening Day 1 visit, at Day 0 (following injection) and at Days 1, 14, 28	
Anthropometric Measurements: weight, height (screening only), BMI, waist circumference , hip circumference	At screening Day 1 visit, screening Day 2, clinic admission visit (Day-1) and at Day 28	Every 28 days. On Days 56, 84, 112, 140, 168
Weight – measured at home by the subjects at morning (8-12h fast) and at bedtime	At Days 7, 14 and 21	Every week when not visiting the site
Draize Score at the Injected Site	At screening Day 1 and at Days 0 (pre- and following injection), 1, 7, 14, 21, 28	Every 28 days.
Serology assays (HBV, HCV and HIV)	At screening day1 visit	
Urine drug screen	At screening Day 1 visit and at clinic admission visit (Day -1)	
Serum chemistry	At screening Day 1, at clinic admission visit (Day -1) and at Day 1, 3, 7, 14 and 28	
Hematology	At screening Day 1, at clinic admission visit (Day -1) and at Day 1, 3, 7, 14 and 28	
Fasting Glucose	At screening Day 1	
Fasting Glucose, Insulin, Leptin, Lipid Profile and FFA	At clinic admission visit (Day -1) and at Day 28	Every 28 days. On Days 56, 84, 112, 140, 168
Urinalysis	At screening Day 1 visit and at Days 14, 28	

Information	Timeframe	Follow-up Timeframe
Cytokines and inflammatory markers– in subjects from the 2nd, 3rd and 4th cohorts	At clinic admission visit (Day -1) visit and at Days 7, 14, 21 and 28	
Histamine	At clinic admission visit (Day -1), and at Day 1, 3 and 14	
Pharmacokinetics in subjects from all cohorts	At Day 0-1	
Photography of the Injected Sites	At screening Day 1 visit and at Days 1, 7, 14, 21, 28	Every 28 days. On Days 56, 84, 112, 140, 168
Thermal Imaging	At screening Day 1 visit,at clinic admission visit (Day -1)and at Days 1, 7, 14, 21, 28	On Day 56
Thermal Imaging - in subjects from the 3rd and 4th cohorts (or in cohort 2 if 2 subjects experience intolerable side effects within the 3rd cohort)		Every 28 days. On Days 56, 84, 112, 140, 168
MRI	At screening Day 2 and at Day 28	
MRI - in subjects from the 2nd cohort		On Day 56
MRI - in subjects from the 3rd and 4th cohorts (or in cohort 2 if 2 subjects experience intolerable side effects within the 3rd cohort)		Every 28 days. On Days 56, 84, 112, 140, 168
Biopsy – in subjects from the 3rd cohort or in cohort 2 if 2 subjects experience intolerable side effects within the 3rd cohort		On Day 56
AE Assessment	At Days 1, 3, 7, 14, 21, 28	Every 28 days
Cohorts 1 and 2: AE Assessment by phone	Days 84 and 112	

6.2.5. Subject Site Visits

Subject site visits will be performed ± 1 days from scheduled date for study visits Day 0-28 and 2± 1 days from schedule date for follow-up visits (Day 56-168). All data relevant for the visit needs to be obtained within 3 days (e.g., blood tests) of visit.

Subject sites visits will include procedures as described in Appendix I - Trial Schedule of Events.

For site visit that results in study discontinuation, see termination visit in Section 6.2.6.

6.2.6. Termination Visit

Once study is discontinued, all reasonable measures should be taken to perform a termination visit. Termination visit should include all procedures necessary to complete subjects' records: AE reporting, any clinical laboratory test needed to evaluate unresolved AEs, evaluation of response, recovery of all clinical supplies and compliance diaries, and updating of subject contact information.

6.2.7. Unscheduled Visit

Unscheduled visits will be performed upon investigator's discretion, upon Sponsor request to redo tests with unusual results or complete missing results and may occur upon subject's decision with no notification in advance. Unscheduled visits will include any study procedure deemed necessary, as described in Section 6.1.

7. SAFETY CONSIDERATIONS AND GUIDANCE FOR INVESTIGATORS

Adherence to protocol monitoring procedures along with the following safety guidance will aid and promote subject safety.

7.1. STUDY RESTRICTIONS REGARDING CONCOMITANT MEDICATIONS

Subjects may not receive the following medications while on study:

- Chronic treatment with systemic steroids or immunosuppressive drugs.
- Chronic treatment with Non Steroid Anti-Inflammatory Drugs (NSAIDs).
- Any investigational product other than RZL-012.

Before dosing, analgesic gels such as Lidocaine or Pramoxine should be used to numb the injected site. An ice pack may be applied on the site of injection following dosing to help reduce pain. At day 3 following blood sampling for histamine, the anti-histamine Benadryl Gel (Dimethindene Maleate 0.1 %) for topical use only should be initiated according to drug instructions for use to avoid itching in the injected area. Benadryl Gel should be applied for 7 days.

Use of supplements or complementary medicines/botanicals and high energy supplements or drinks is prohibited, except for conventional multivitamin supplements.

7.2. SAFETY MEASUREMENTS

Simple measures may help avoid specific AEs associated with the use of the RZL-012 investigational product. Thus, study subjects must be informed of possible AEs that occurred in animal studies (rats and pigs):

- Any injection site reaction may occur. Pain, swelling, itching, edema, erythema, hematoma etc.
- Slight transient injection site bleeding following injection may occur.
- Itching in the injected area may occur, and study subjects should be advised to use an antihistamine gel for topical use according to drug recommendations, wear wide cotton shirts, prevent touch with irritable clothing, avoid scratching and avoid exposure to direct sun. Itching is expected till 7 days following drug injection.
- Local erythema in the injected area.
- Local heat in the injection area.
- Study restrictions regarding concomitant medications are listed in Section 7.1.
- The local subcutaneous fat reduction may appear as a slight dip in the skin surface. This decline may be temporary and transient.
- Transient increase (72%) in the WBC count by 24 hours following injection, which returned to basal level after 14 days. Probably associated with the inflammatory response at the site of injection and involve neutrophils, monocytes and eosinophils.
- Increased level of BUN and of creatinine and minimal single cell necrosis was observed in tubular epithelium at cortico medullary junction of kidney in rats receiving a dose higher 25 times the highest dose in this study. All abnormalities were found to be reversible by Day 14.
- Increased AST level which is most typical of myofiber injury associated with study related procedures. This elevation was found to be reversible by Day 14.
- Transient increase of serum CRP levels (in rats) which returned to the basic level by 14 days.
- Marked irritancy in the injected subcutaneous tissue resulting in coagulation necrosis of relatively large areas in the subcutaneous tissue planes acutely. Necrosis persisted for up to 14 days and was accompanied by early evidence of healing in the form of chronic inflammation and fibrosis.
- Local inflammation (minimal to moderate) with muscle degeneration, epidermal/dermal necrosis (minimal to severe) and parakeratosis (minimal). Inflammation observed at injection site was also extended to adjacent subcutaneous adipose tissue. By 56 days the inflammation was minimal, muscle degeneration was not evident and inflammation to adjacent subcutaneous adipose tissue was present.
- A slight elevation in body temperatures was noted in male pigs.
- Sinus tachycardia (in pigs), occurring at the 4 hour interval post dosing.
- In addition, other acceptable treatment to relieve drug-related AE's should be used at Investigator's discretion.

Study subjects must be informed of possible AEs that occurred in clinical studies (phase 0):

- At the injection site -local and transient: erythema, oedema, pruritus, anesthesia, pain, mass (subcutaneous scar).
- Abdominal abscess

- Transient moderate to severe elevation of the liver enzymes: Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST).

7.3. PREMATURE DISCONTINUATION FROM STUDY

Study will be prematurely discontinued in any of the following cases:

- Subject's request.
- Any life-threatening (i.e., Grade 4) adverse event may cause prematurely discontinuation.
- Systemic hypersensitivity reaction may cause prematurely discontinuation.
- Any Grade 3 or 4 ADR (defined in Section 9.3) clinically evaluated by the PI and/or Sponsor as warranting subject discontinuation.
- Non-compliance: Subject's non-compliance with study procedures as evaluated by PI and/or Sponsor as warranting subject discontinuation.
- Other reasons regarded by PI as warranting subject's discontinuation.
- Premature study termination as described in Section 7.4.

Subjects who discontinue the study prematurely will be queried whether an adverse event contributed to their decision.

7.4. PREMATURE STUDY TERMINATION

The study will be prematurely terminated in any of the following cases:

- Recurring serious or severe ADR (defined in Section 9.1) clinically evaluated by PI and/or Sponsor as warranting study termination.
- A decision made by Sponsor and/or IRB/EC and/or local regulatory agency to terminate the study.

7.5. DEVIATION FROM STUDY PROTOCOL

The investigator shall not deviate from the study protocol without first obtaining a written approval from the Sponsor, or its official designee, and if applicable, from the local IRB/EC according to local regulations.

In the event of medical emergencies, the investigator shall use appropriate medical judgment and will remove the subject from any immediate hazard, then notify the Sponsor or its official designee and if applicable, the local IRB/EC, within 2 days, of the type of emergency and course of action taken.

Any other changes to or deviations from the protocol will be made as an amendment to the protocol and must be approved by the Sponsor or its official designee and the local IRB/EC before they can be implemented. Accordingly, the Sponsor will not assume responsibility or liability for any unauthorized deviation from or change to the protocol.

8. INVESTIGATIONAL PRODUCT AND VEHICLE SPECIFICATIONS

8.1. DESCRIPTION OF RZL-012

RZL-012 investigational drug is intended for a single dose in multiple injections into the subcutaneous fat. The injection dosing regimen and technique is crucial for the therapy safety and efficacy.

8.2. FORMULATION, PACKAGING AND LABELING

The RZL-012 drug is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 250 mg/4.8 mL RZL-012 in formulation F12.

The vehicle is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 1 mL of formulation F12.

8.3. STORAGE AND STABILITY OF RZL-012 AND VEHICLE

The RZL-012 and vehicle kits will be stored in the site pharmacy at monitored room temperature conditions (22 ± 7 °C) protected from light. Storage space will be separate, designated and adequately labeled as containing investigational product.

Stability program of RZL-012 is ongoing and site inventory will be managed by the Sponsor according to accumulating stability data. Suitability of the product's expiration date must take into consideration and comply with FIFO (First In First Out) principals.

The storage conditions are summarized in Table 3.

Table 3: RZL-012 and Vehicle Storage Conditions

Storage Conditions	**Maximal Storage Duration**
Individual vials: Room temperature (15-30 °C)	According to expiration date as will be provided by manufacturer.
* Stability program for RZL-012 is ongoing and site inventory will be managed by the Sponsor according to accumulating stability data.	

8.4. DOSAGE, DISPENSING AND ADMINISTRATION OF RZL-012 AND VEHICLE

8.4.1. Dosage

RZL-012 therapy is available in vials of 250 mg/4.8 mL.

The vehicle is available in vials of 4.8 mL.

8.4.2. Administration and Instructions for Use

Each individual vial must be kept and handled at room temperature.

The vial should be manually shaken before consumption.

1 mL Luer-lock syringes with RZL-012 solution should be filled with 30 G 1/2" sterile needle as described below:

- Cohort 1: 8 x 0.1 mL/syringe/subject
- Cohort 2: 16 x 0.1 mL/syringe/subject
- Cohort 3: 24 x 0.1 mL/syringe/subject
- Cohort 4: 36 x 0.1 mL/syringe/subject

One vial may be used for dosing of two subjects that are dosed together. Dosing of both subjects will be within a maximum of 4 hours. If only one subject is to be dosed, a single vial will be administered to that subject. Breached vials will not be re-used for other subjects. Each vial must be placed back into the container. All open vials must be kept until the end of the study for the Sponsor to decide either to discard or return to the Sponsor.

8.5. ACCOUNTABILITY OF RZL-012 AND VEHICLE

The RZL-012 investigational product was manufactured by PharmaCore (USA) and complies with cGMP requirements. Formulation and packing was done by Nextar (Israel) and complies with cGMP requirements.

The vehicle was manufactured and packed by FusionRx (USA) and complies with cGMP requirements.

The RZL-012 investigational product and vehicle will be supplied in kits, in quantities as needed to comply with the treatment of site subjects according to the study protocol.

Site coordinator will notify the Sponsor or its official designee, in a timely manner and no less than 14 working days in advance, of any supply requirements to prevent shortage.

Shipment, storage and inventory documentation will be updated regularly and kept in the investigation files at the site to allow inspection and trace of the supplied product.

9. ADVERSE EVENTS

9.1. ADVERSE EVENT DEFINITIONS

9.1.1. Definition of Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

9.1.2. Definition of Serious Adverse Event

A SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening AE, as defined below
- subject hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect
- important medical event, as defined below

A life-threatening AE is any AE that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death).

An important medical event is an AE that may not result in death, be life-threatening, or require hospitalization but may be considered a serious AE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. It can also include AEs otherwise judged to be serious by either the investigator or the Sponsor.

9.1.3. Definition of Adverse Drug Reaction

AEs associated with the use of investigational product (i.e., probably or possibly related to treatment as defined in Section 9.3) are also termed Adverse Drug Reactions (ADRs).

9.2. ADVERSE EVENT GRADING

AE will be documented and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 June 14, 2010) (10).

AE that do not appear in the CTCAE will be graded as follows:

- Mild (Grade 1): Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
- Moderate (Grade 2): Sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
- Severe (Grade 3): Sign or symptom that is intense or debilitating and that interferes with usual activities and/or requires hospitalization. Recovery is usually aided by therapeutic measures and the discontinuation of the study product may be required.
- Life-threatening or disabling (Grade 4): Sign or symptom that is Life-threatening or disabling.
- Death (Grade 5): Death related to AE

9.3. CAUSALITY ASSESSMENT OF ADVERSE EVENTS (AEs)

All AEs will be evaluated by the investigator and assigned an estimated relationship to the RZL-012 investigational product. The terms "probable", "possible", "unlikely", or "unrelated" refer to the association with the use of the investigational product, as defined below in Table 4.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Assessment of causal relationship should be recorded directly in subjects CRF.

Definition of AEs causality is specified in the table below (Table 4).

Table 4: Definition of Causality

TERM	DEFINITION	CLARIFICATION
Unrelated	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
Unlikely Related	In general, this category can be considered applicable to those AEs, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study procedures/ investigational product.	An AE may be considered unlikely related if or when (must have two): ▪ It does not follow a reasonable temporal sequence from the study procedures/administration of the investigational product. ▪ It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It does not follow a known pattern of response to the study procedures/investigational product.
Possibly Related	This category applies to those AEs for which, after careful medical consideration at the time they are	An AE may be considered possibly related if or when (at least two of the following):

TERM	DEFINITION	CLARIFICATION
	evaluated, a connection with the study procedures/investigational product administration appears unlikely but cannot be ruled out with certainty.	▪ It follows a reasonable temporal sequence from study procedures/administration of the investigational product. ▪ A causal relationship to the experimental treatment cannot necessarily be reasonably excluded and an alternative explanation (e.g., concomitant investigational product or concomitant disease) cannot be reasonably suggested as causing the treatment emergent AE ▪ It follows a known pattern of response to the study procedures/ investigational product.
Probably Related	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with a high degree of certainty to be related to the study procedures/investigational product.	An AE may be considered probably related if or when (at least three of the following): ▪ It follows a reasonable temporal sequence from study procedures/administration of the investigational product. ▪ It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the investigational product, yet investigational product-relatedness clearly exists. ▪ It follows a known pattern of response to the study procedures/investigational product.
Definitely Related	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with definite certainty to be related to the study procedures/investigational product.	An AE may be considered definitely related if or when all of the following apply: ▪ It follows a reasonable temporal sequence from study procedures/administration of the investigational product. ▪ It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the investigational product, yet investigational product-relatedness clearly exists. ▪ It follows a known pattern of response to the study procedures/investigational product.

*In this protocol Unlikely is deemed as Unrelated.

9.4. UNEXPECTEDNESS OF ADVERSE DRUG REACTIONS

An ADR is considered unexpected when its nature or severity is not consistent with the applicable product information (i.e., RZL-012 Investigator's Brochure).

9.5. ADVERSE EVENT REPORTING AND MONITORING REQUIREMENTS

9.5.1. General

All adverse events, serious and non-serious, will be fully documented in both source documents and CRFs as described in Section 6.1.16, and each AE will be assessed in light of its clinical significance. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship to the investigational drug, i.e., causality assessment, for each AE.

Any AE occurring prior to initiation of first dose, after initiation of the first dose and or during any point throughout the study should be recorded on the Adverse Event page of the CRF. All adverse events occurring until subject is terminated from the study (28 days after the injection of RZL-012 and in the highest dose cohort until 6 months from injection of RZL-012), should be captured in the CRF. AEs should be recorded in the CRF using the medical terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

Occurrence of any Grade 4 and Grade 3 or 4 ADR must warrant clinical evaluation by the treating investigator and reported to the Sponsor within 7 calendar days.

ADRs graded > 1 will be followed-up until resolution, or for a maximal duration of 6 months after RZL-012 injection, whichever occurs first.

9.5.2. SAE Reporting

The PI or his designee must report to the Sponsor any SAE occurring after injection of the study treatment, regardless of their relationship to the investigational product.

Sponsor contact details for SAE reporting:

Sharon Perles, sharon.perles@raziel-therapy.com, fax: 972-2-625-0901.

An initial report must be faxed or emailed to sharon.perles@raziel-therapy.com, fax: 972-2-625-0901 within 24 hours of becoming aware of the event and must include SAE general description, start date, end date (if applicable), the reason for evaluation as a SAE, basic subject information, assessment of the relationship to the investigational product, expectedness, and study therapy information.

Follow-up information, including outcome, and treatment shall be faxed or emailed within 48 hours. Source documents to support the SAE (e.g., discharge summary, test results) shall be included in the report.

A complete SAE report must be sent to the Sponsor at the first possible date and no later than 7 calendar days after SAE end date. In addition to the information described in the initial report, this report will include AE common terminology criteria (CTC) description and grading, treatment given (if applicable), SAE outcome, an assessment of the relationship to the investigational product, and expectedness.

SAE will be recorded on designated CRF forms in a timely manner and no later than 7 calendar days after its end date.

The PI or his designee will submit the SAE report to IRB/EC according to applicable local regulations and will update the Sponsor.

9.5.3. Expedited Reporting

Expedited reporting by PI to IRB/EC is warranted for all Suspected Unexpected Serious Adverse Reactions (SUSAR), i.e., unexpected SAEs that are considered related to study product as defined in Sections 9.1.2, 9.1.3, and 9.4). Additional cases will be communicated by PI to IRB/EC via expedited reporting when required by local regulation.

Expedited reports will be submitted to the applicable regulatory authorities by the Sponsor or designee within the required timelines according to local regulations.

Any pregnancy of a partner of a study male subject after dosing is considered an immediately reportable event.

Such events must be reported within one (1) working day of the investigator becoming aware of the event. Pregnancies shall be followed for the duration of the pregnancy. It is the PI's responsibility to provide to the Sponsor follow-up information on the outcome of the pregnancy including information about any sequelae.

10. STATISTICAL CONSIDERATIONS

10.1. STUDY DESIGN AND OBJECTIVE

The purpose of this phase 2a study is to find the tolerated dose that provides the largest thermogenic effect.

The study is designed as a randomized, double-blind, two-arm clinical trial. Eligible subjects will be randomized to receive either RZL-012 or placebo (vehicle). In this feasibility study, different parameters of efficacy assessment will be measured in the all dose groups for a maximum period of up to 6 months. Subject follow-up for safety will be up to 112 days after treatment administration for the two lower doses cohorts and up to 168 days after treatment administration for the last two highest dose cohorts or up to 112 as the first 2 cohorts in case of termination before visit Day 112.

10.2. STUDY ENDPOINTS

10.2.1. Primary Safety Endpoint

The main objective is the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat. Therefore, the primary safety endpoint will be the incidence of intolerable side effects and all adverse events of RZL-012 injection into the subcutaneous fat. The dose escalation scheme will be stopped if at any dose cohort, 2 patients will experience intolerable side effects.

10.2.2. Primary Efficacy Endpoint

The primary endpoint for efficacy is a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera. A thermogenic effect is defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the non-injected site, apparent at least 28 days after injection and non-related to inflammatory response as determined by inflammatory cytokines. The primary efficacy evaluation will be supported by results from secondary endpoints, including MRI, biopsy and biomarkers

10.2.3. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Duration of the thermogenic effect, defined as a net-delta ≥ 1.
- Local reduction in fat mass as determined by MRI.
- Clinical laboratory changes from baseline in:
    - Fasting blood glucose,
    - Triglycerides (TG),
    - High-density lipoprotein (HDL),
    - Low-density lipoprotein (LDL),
    - Total-cholesterol (TC), and
    - Free-fatty-acids (FFA).
- Pharmacokinetic profile for RZL-012.
- Anthropometric changes from baseline in:
    - Body weight,
    - BMI,
    - Waist circumference, and

  - WHR.

- Change from baseline in inflammatory markers and cytokines:
  - CRP,
  - Adiponectin,
  - CD-163,
  - Interleukin (IL)-1β,
  - IL-4, IL-6,
  - IL-10,
  - IL12p70,
  - IL-13,
  - IL-23,
  - Tumor necrosis factor (TNF) α and
  - TGFβ1.
- Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site.

10.2.4. Safety and Tolerability Endpoints

Safety endpoints include:

- Incidence of AEs and SAEs, by severity and relation to study treatment. AEs will be coded using MedDRA version 19.1 (or higher).
- Physical examination (including Draize score)
- Vital signs
- Blood laboratory tests
- ECG

10.3. SAMPLE SIZE JUSTIFICATION

This study is planned as a dose escalation study following a 6 subjects per dose group paradigm with the addition of a 2 subjects vehicle control group for the 2 all doses. A maximum of 32 evaluable subjects will be included in the study (24 in the RZL-012 treatment arm and 8 in the placebo arm) and followed for as long as 3 months in the 2 lowest dose cohorts, and in the 2 highest dose cohorts for up to 5 months.

10.4. ANALYSIS SETS

10.4.1. Safety Analysis Set (SA)

The safety analysis set (SA) will consist of all enrolled subjects who received the study treatment, either RZL-012 or placebo (exposed population), including subjects prematurely withdrawn.

All enrolled subjects receiving at least one study drug injection are considered evaluable for the SA set.

10.4.2. Efficacy Analysis Set (EF)

The efficacy (EF) will consist of all subjects from the SA analysis set without any major protocol violations measured at baseline. Subjects will be analyzed according to the treatment received.

10.4.3. PK (PKA) Analysis Set

The PK analysis set will consist of all subjects with no major deviations related to study drug administration (e.g., incomplete injection of study drug).

10.4.4. Statistical Analysis of Analysis Sets

The SA analysis set will serve as the principal data analysis set for the analyses of the safety endpoints.

The EF analysis set will serve as the principal data analysis set for the analyses of the efficacy endpoints.

The PK analysis set will serve as the principal data analysis set for the PK analysis.

10.5. STATISTICAL ANALYSIS

10.5.1. General

Statistical analysis will be performed using SAS V9.4 or higher (SAS Institute, Cary NC, USA).

Statistical analyses will be mainly descriptive in nature where study data will be tabulated and summarized using the mean, standard deviation or standard error, median, minimum, maximum and number of subjects by cohort for continuous data. For categorical data, results will be summarized via a count and percentage by cohort. The effects of noncompliance, dropouts, and covariates, may be assessed to determine the impact on the general applicability of results from this study.

If any statistical tests are performed, they will be two-sided. The required significance level of findings will be equal to or lower than 5%. Nominal p-values will be presented.

Where confidence limits are appropriate, the confidence level will be 95%.

10.5.2. Subject Disposition

A detailed description of subject accountability including count of subjects included, randomized, exposed, completed (i.e., subjects who complete the study treatment) and discontinued along with the main reason for discontinuation will be generated for each cohort and for all subjects. All withdrawals from the study, taking place on or after study drug injection, will be fully documented in the body of the Clinical Study Report.

Note that the actual study duration is for a period of maximum 6 months, with efficacy analyses being conducted at 28 days and 56 days for all dose levels and up to 6 months for the 3rd and 4th cohorts or for the highest dose level achieved.

10.5.3. Demographic and Baseline Characteristics

Baseline will be defined as the last available and evaluable parameter value before and closest to the injection. If a rechecked value is used for baseline, it should be collected under the same conditions as for the planned baseline (e.g., fasting condition).

Baseline safety data will be presented along with subsequent safety values assessed during or after dosing.

10.5.4. Primary Safety Endpoint

The incidence of intolerable side effects will be presented by treatment overall and by cohort along with two sided 95% exact binomial Confidence Interval (CI).

The incidence of all adverse events will be presented by treatment overall and by cohort along with two sided 95% exact binomial Confidence Interval (CI).

10.5.5. Efficacy Analysis

The average temperature will be presented in a tabular form by visit, site (treated / not treated) and treatment received (RZL-012 / placebo) by cohort and overall. Difference between the sites (treated – not treated) will be presented in a tabular form by visit treatment along with the change from baseline (net-delta) in these differences by cohort and overall.

Non-parametric tests will be used to compare the net-delta between the study arms for the relevant cohorts and visits.

The number and percent of subjects with a thermogenic effect, defined as a net-delta ≥ 1, will be presented by cohort and visit for the subjects in the active arm. The duration of the thermogenic effect after the Day 28 visit, for subjects in the active arm with thermogenic effect at the Day 28 visit will be presented.

Subcutaneous Fat Mass (SFM) ratio (treated sites / control sites) averaged over the MRI slices will be presented in tabular form by visit, treatment and cohort. The change from baseline in this ratio (in % from the ratio at baseline) will be presented in the same manner, and compared between the treatment arms with non-parametric tests.

Changes from baseline in fasting blood glucose, lipid profile, anthropometric changes, inflammatory markers and cytokines will be presented by visit, treatment, and cohort.

Histology results will be presented in tabular form by treatment.

10.5.6. Pharmacokinetics (PK) Assessment

PK profile will be assessed as described below, and presented in a tabular form. Individual PK parameters will also be presented in a listing.

PK profile will be assessed by: C_{max}, T_{max} (time of maximum observed sample concentration) and if appropriate AUC values for the test article and from concentration-time data.

Based on the data, appropriate parameters will be estimated and may include, C_0/Dose and/or C_{max}/Dose, $AUC_{(Tlast)}$ (area under the concentration-time curve from time zero to the time of final quantifiable sample), $AUC_{(0-t)}$ (area under the concentration-time curve from time zero to t, where t denotes a specific sample time following dosing), and AUC/Dose. Based on the data, additional secondary parameters will be calculated, if appropriate, and include, AUC_{INF} (area under the concentration-time curve from time zero extrapolated to infinity), and $T_{1/2}$ (terminal half-life).

10.5.7. Safety and Tolerability

Safety analyses will be descriptive in nature.

All reported adverse events will be coded to a standard set of terms using MedDRA coding dictionary (V19.1 or higher) treatment.

AEs and tolerability data will be presented descriptively by treatment and cohort. AEs will be tabulated by body system, preferred term, seriousness, severity and relation to study drug by cohort. Where applicable, changes in values over time (e.g., lab values, vital signs, electrocardiograms [ECGs]) will be presented, this will include clinical laboratory evaluations (including CBC, blood chemistry and urinalysis), coagulation (INR, PTT, PT), cytokines, vital signs, and ECGs. Shift tables of normal / abnormal versus baseline may be presented as well.

Draize scores will be presented in tabular format by visit, treatment, and cohort.

10.6. HANDLING OF MISSING DATA

No imputation of missing data will be performed.

10.7. INTERIM ANALYSIS

An interim analysis is planned at the end of each cohort for evaluation of efficacy. For this purpose, a data lock (except for externally collected data such as PK) will be implemented after each cohort is completed. Upon lack of trends in efficacy due to effect size, the Sponsor will consider study termination.

11. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

11.1. DATA COLLECTION AND REPORTING

Each study subject will be assigned an individual CRF that will contain all of the relevant study information. The investigator shall ensure that all data is completely and accurately recorded on the CRFs throughout trial duration.

Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

All fields and blanks in the CRFs will be completed. The following abbreviations are to be used when values or answers are not available: NA = Not applicable, ND = Not done, UNK = Unknown, CONT = Continued.

White-out or erasure on the CRF is not permitted under any circumstances. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained). If an entry on a CRF form is changed, the correction will be made as follows: A single line will be drawn through the incorrect entry, the date and initials of the reporting individual will be added beside the entered change and/or correction, and an explanation will be added when applicable.

When a subject withdraws from the study, regardless of cause, all final study evaluations should be attempted.

If a subject is lost to follow-up, (i.e., fails to return for scheduled visits) every reasonable effort must be made to contact the subject in order to determine why the subject failed to return. All actions taken in this regard will be documented and dated in the CRF.

Once completed, a copy of each completed CRF will be signed and dated by the investigator or a designated representative and submitted to the Sponsor.

11.2. RECORD KEEPING

The investigator will maintain all records for this study including medical records, laboratory reports, informed consent forms, safety reports, subjects' CRF, and any other pertinent data. All records are to be retained by the investigator for a period of fifteen years after completion of the study.

11.3. SOURCE DATA AND SOURCE DOCUMENTS

ICH-GCP defines source data as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are defined as original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, subject files, and records kept at departments involved in the clinical trial, etc.).

The following data is to be recorded directly on the RZL-012 trial forms or CRF which will be considered to be the source data:

- Subjects' weight diaries.
- Subjects' questioning, e.g., pain, itching, topical antihistamine application.
- Assessment of AEs relation to investigational product, i.e., causality assessment, and expectedness reported by investigator.

The investigator should maintain the trial's essential documents as required by ICH-GCP guidelines and the applicable regulatory requirements, and take measures to prevent accidental or premature destruction of these documents.

Upon request of the monitor, auditor, IRB/EC, or regulatory authority, the investigator will ensure direct access all requested trial-related records.

11.4. STUDY MONITORING

Monitoring procedures are required to assure compliance to ICH-GCP guidelines, the study protocol and local regulations.

The investigator shall allow the Sponsor or its official designee to monitor and audit periodically, at mutually convenient times, all CRF and corresponding subject records. The monitoring schedule will be based on Sponsor’s monitoring plan and will be done by competent monitors per GCP by either Sponsor personnel or sponsor’s designee such as CRO.

11.5. CONFIDENTIALITY, DATA DISCLOSURE, AND PUBLICATION

In order to protect subject confidentiality, a consecutive identification number will be attributed to each subject enrolled to the trial. In order to avoid identification errors, this number and subject's initials (first letter of first name and the first letters of surname) will identify the subject and must be included on all CRFs. The investigator will complete subject identification on a confidential site log, which will be used for subjects' traceability and follow-up.

Individual subject medical information obtained as a result of this study is to be considered confidential and disclosure to third parties other than the regulatory authorities, or other persons or organizations designated by the Sponsor, is prohibited. Any medical information may be provided to the subject's personal physician or to appropriate medical personnel responsible for the subject's care. Additionally, data generated from this study is to be provided, upon request, to the Sponsor's monitors, as well as to the local IRB/EC. Subject confidentiality is to be further assured by utilizing subject identification code numbers to identify subject data.

All information supplied by Raziel Therapeutics Ltd. in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, the Investigators' Brochure, clinical protocol, CRF, and other scientific data. Any data collected during the study are also considered confidential. This confidential information shall remain the sole property of Raziel Therapeutics Ltd, shall not be disclosed to others without the written consent of the Sponsor, and shall not be used except in the performance of this study. The information developed during the conduct of this clinical study is also considered confidential, and will be used by the Sponsor in connection with the development of the product. The information may be disclosed as deemed necessary by the Sponsor. To allow the use of the information derived from this clinical study, the investigator is obliged to provide Raziel Therapeutics Ltd. with complete test results and all data developed in this study.

The Sponsor has full ownership of the original case report forms completed as part of the study.

By signing the clinical study protocol, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The information obtained during this study may be made available to other investigators who are conducting similar studies.

It is agreed that, consistent with scientific standards, publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol.

Raziel Therapeutics Ltd. will disclose the results of the trial on the basis of the final analysis and following the revision of a draft manuscript by the investigators, unless posting would compromise publication in a peer-reviewed medical journal or contravene national laws or

regulations. Study results may also be disclosed through presentations and abstract submissions at professional scientific meetings.

12. HUMAN SUBJECTS

12.1. DECLARATION OF HELSINKI

Both the PI and the Sponsor will ensure that the study is conducted in agreement with the Declaration of Helsinki, ICH Guideline for Good Clinical Practice (ICH-GCP), and the local laws and regulation.

12.2. INFORMED CONSENT

As described in Section 6.1.1.

12.2.1. LIABILITY AND INSURANCE CONDITIONS

Raziel Therapeutics Ltd. holds a clinical trial liability insurance policy.

A copy of the policy summary will be filled in the investigator's site file.

13. REFERENCES

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10. NIH. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 2010 [Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Appendix I: Trial Schedule of Events

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Signed informed consent	X										
Medical history	X		X								
Complete physical exam	X									X	
Serology assays (HBV, HCV, HIV)	X										
Fasting glucose	X		X								
Fasting glucose, insulin, leptin and lipid profile (including FFA)			X							X	Every 28 days
Inflammatory markers and Cytokines - In subject of the 2nd, 3rd and 4th cohorts [b]			X				X	X	X	X	
Photography of site of injection and contralateral	X				X		X	X	X	X	Every 28 days
MRI section around the umbilicus		X								X	
MRI section around the umbilicus – for cohort 2											On Day 56

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts[1] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
MRI section around the umbilicus – for 3rd and 4th cohort or in cohort 2 if 2 subject experience intolerable side effects in cohort 3)											Every 28 days
Anthropometric measurements: (weight, height) BMI, (waist & hip circumference) WHR	X	X	X							X	Every 28 days
Weight – by the subjects at home – morning(8-12hr overnight fast) and evening							X	X	X		On weeks when not visiting the site
Urine Drug Screen	X		X								
Infra-Red thermal imaging of the injected site	X		X		X		X	X	X	X	On Day 56

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts[l] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Infra-Red thermal imaging of the injected site -for 3rd and 4th cohort or in cohort 2 if 2 subjects experience intolerable side effects will in cohort 3)[k]											Every 28 days
Serum Chemistry, Hematology [c]	X		X		X	X	X	X		X	
Histamine levels[d]			X		X	X		X			
Urinalysis	X							X		X	
Pharmacokinetics [f]				Pre [e] X post [e]	X						
Draize score at the injected site [g]	X			Pre [e] X post [e]	X		X	X	X	X	Every 28 days
Vital signs [h]	X			Pre [e] X post [e]	X		X	X	X	X	
Injection of RZL-012				X							
ECG [i]	X			X post [e]	X			X		X	
Pulse rate [j]				Pre [e] X post [e]	X						
Adverse event assessment					X----------→						Every 28 days

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts[1] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Adverse event assessment by phone for cohorts 1 and 2											On Day 84 and 112
Subjects diary recording weight							X	X	X		On weeks when not visiting the site
Biopsy – In subject of cohort 3 (or in cohort 2 if 2 subjects experience intolerable side effects in cohort 3)[k,l]											On Day 56

a. Study day is based on Day 0 defined as the day of RZL-012 injection.

b. Inflammatory markers and cytokines from the 2nd, 3rd and 4th cohorts (on 6 RZL-012 treated and 2 placebo treated subjects in each cohort)**: CRP,** Adiponectin, CD-163, Interleukin [IL]-1β, IL-4, IL-6, IL-10, IL12p70, IL-13, IL-23, Tumor necrosis factor [TNF] α and TGFβ1.

c. CBC, coagulation, serum chemistry analysis, renal and liver function , urinalysis, CPK, amylase measurement: before injection,14d and 28d following injection

d. Histamine blood level measurement: clinical admission, following drug injection (24h ± 2h), 3d and 14d following injection

e. Pre/post – refers to before/after injection respectively

f. Pharmacokinetics at the given time points: 0, 30, 60 min, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 30h in subjects from all cohorts. Pharmacokinetics will not be conducted in the fourth cohort as the injected dose is divided in 2 clusters 2 weeks apart.

g. Draize score evaluation: before injection, 2h, 24h and 7d,14d,21d and 28d following injection

h. Vital signs measurement: before injection, 2h, 24h and 7d,14d,21d and 28d following injection

i. ECG is to be performed in triplicate for all measurements in given time point: 4h, 12h, 24h, Day 14 and 28 following injection

j. Pulse rate measurements at given time points: 1h, 2h, 4h, 8h, 12h, 24h following injection in the opposite hand of blood sampling

k. For 3 subjects of cohort 3 (in cohort 2 if 2 subjects experience intolerable side effects in cohort 3) - if thermogenesis is evident by thermal camera by Day 56, biopsy from the injected for histology and BAT characterization**.**

l. For subjects from the 3rd (or in cohort 2 if 2 subjects will experience intolerable side effects within the 3rd cohort) and 4th cohort