RAZIEL THERAPEUTICS LTD.

INVESTIGATIONAL NEW DRUG PROTOCOL

RZL-012

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VERSION 1.1
30 MAY 2022

A DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 2 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF RZL-012 TREATMENT IN SUBJECTS SEEKING FAT REDUCTION IN THE FLANKS

SPONSOR:

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
cm	Centimeter
CNS	Central nervous system
CRF	Case report form
CV	Coefficient of variable
DD	Dercum's disease
ECG	Electrocardiograms
FDA	Food and Drug Administration
FSH	Follicle-Stimulating Hormone
GAIS	Global Aesthetics Improvement Scale
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IND	Investigational New Drug
INR	International normalized ratio
IRB/EC	Institutional Review Board/Ethics Committee

ABBREVIATION	DEFINITION
kg	Kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MOA	Mechanism of action
MRI	Magnetic resonance imaging
N	Number of subjects
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Partial thromboplastin time
QOL	Quality of life
RBC	Red blood count
SAE	Serious adverse event
SFM	Subcutaneous Fat Mass
SMF	Submental fat
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event(s)
US/USA	United States of America
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary

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 STATEMENT

I have read and understand 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 maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

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

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form (ICF) 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 IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved 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, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 11.0 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the Medical Monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor, Raziel Therapeutics Ltd. (Raziel) and its agents, as well as the United States (U.S.) 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).

This protocol contains information that is proprietary to Raziel. The information contained herein is provided for the purpose of conducting a clinical trial for Raziel.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of Raziel.

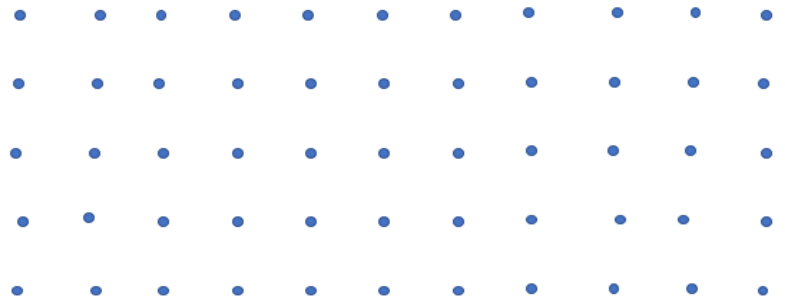
Investigator's Name	Investigator's Signature	Date

PROTOCOL SYNOPSIS

Study Title	A Phase 2 Clinical Trial Comprised of a Double-Blind, Placebo-Controlled Phase Followed by An Open-Label Phase to Evaluate the Safety and Efficacy of RZL-012 in Subjects Seeking Fat Reduction in the Flanks (RZL-012-FL-P2US-001)
Phase	Phase 2
Study Drug	RZL-012
Study Objectives and Endpoints	Primary Objective: • To assess safety and tolerability of a single RZL-012 injection session into the flank. Secondary Objectives: • To evaluate the efficacy of RZL-012 treatment versus placebo treatment on fat reduction in the flanks • To assess the safety of a second dose of RZL-012 Primary Endpoint: • Evaluate safety following a single injection session of RZL-012 vs. placebo into the flanks based on AEs, laboratory tests, ECG, and skin irritancy Secondary Endpoints: • Comparison of the proportion of flanks having an improvement as indicated by a score of 0 to 6 according to the Physician Global Assessment Scale (GAIS) in RZL-01-treated flanks vs placebo-treated flanks. • Comparison of the proportion of subjects who are satisfied with treatment results as indicated by a yes/no satisfaction questionnaire in RZL-012-treated flanks vs placebo-treated flanks. • Comparison of the mean reduction in volume at 12 weeks post treatment vs. baseline for each of the treated flanks, as measured by 3D images using the Canfield 3D system in RZL-012-treated flanks vs placebo-treated flanks. • Ability of blinded reviewers to correctly identify, per patient, the flank treated with test compound (active) vs the flank treated with vehicle (placebo). Success will be defined as at least 70% correct identification vs the expected 50% correct identification based on random guessing. • Evaluate safety following a second dose of RZL-012 based on AEs, laboratory tests, ECG, and skin irritancy. • Characterization of RZL-012 pharmacokinetic (PK) profile
Study Design	This clinical trial is comprised of a double-blind, placebo-controlled phase followed by an open-label phase. The double-blind, placebo-controlled phase of the trial will consist of a screening period, baseline visit and a 12-week post-treatment follow-up period. At the baseline visit, each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will receive multiple injections in a single session of RZL-012 or placebo. Blood samples will be collected for 6 of the 12 subjects for PK analyses. All subjects will be followed up for 12 weeks after the single treatment session. Upon completion of the double-blind phase of the study, and the opening of codes subjects will be offered RZL-012 open-label treatment in the flank previously

	treated with placebo. Consenting subjects will be followed for safety and efficacy for an additional 12 weeks. In both the double-blind and open-label phases of the study, subjects will be monitored for adverse events (AEs). Subjects will return to the site for visits at 1 week, 4 weeks, 8 weeks, and 12 weeks post treatment and will be monitored for safety and efficacy during these visits. Subjects who will be collected with PK will return to the clinic at Day 1 post injection for further PK samples. The dimensions of flanks will be measured using 3D images and volumetric calculations using Canfield 3D images.
Sample Size	12 subjects, 24 flanks
Study Population	Adult volunteers of age 18 to 65 years with visible and palpable fat in the flanks.
Main Inclusion Criteria	For a subject to be eligible for this study, he or she must meet **all** of the following criteria: 1. Is a male or female subject between the ages of 18 and 65 years, inclusive. 2. Has body mass index (BMI) BMI of ≥ 22 and < 30. 3. Has clearly visible and palpable fat in the flanks 4. Has symmetrical appearance of right and left flanks 5. Agrees to maintain weight (i.e., within 5% of body weight) by not making any changes in diet. 6. Agree to avoid exposure of the treated area to the sun for at least 1 month after each treatment session. 7. If female, is not pregnant or breastfeeding based on the following: a. agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 28 days after the last day of study drug and a negative urine pregnancy test at screening and baseline; or b. is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy); or c. is confirmed postmenopausal status (defined as either having amenorrhea for ≥ 12 consecutive months without another cause, having documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL, or having another documented medical condition (e.g., was born without a uterus)) NOTE: The following are considered highly effective contraceptive methods: hormonal oral contraceptives, injectables, and patches; intrauterine devices; double-barrier methods (synthetic condom, diaphragm, or cervical cap used with spermicidal foam, cream, or gel); and male partner sterilization.

	8. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods, e.g. condom, from study baseline until 7 days after the last day of study drug. 9. Is willing to avoid strenuous exercise for seven (7) days post treatment. 10. Is motivated to adhere to the visit schedule and protocol requirements. 11. Is willing and able to sign an Institutional Review Board (IRB) approved informed consent form (ICF) indicating that they are aware of the investigational nature of the study.
Main Exclusion Criteria	Subjects must **NOT** meet any of the following exclusion criteria to be eligible for enrollment: 1. Is unable to tolerate subcutaneous injections. 2. Has dysfunctional gallbladder activity (e.g., underwent cholecystectomy or cholecystitis). 3. Has an uncontrolled systemic disease that is not stabilized (i.e., cardiovascular disease, mental illness). 4. Has used anticoagulation therapies that may increase bleeding or bruising (i.e., aspirin, ibuprofen, vitamins, and herbal preparations) for seven (7) days prior to treatment. 5. Has medication or a history of coagulopathy. 6. Has a history or family history of venous thrombotic disease. 7. Had a non-invasive fat reduction and/or body contouring procedure in the flanks within the past 12 months. 8. Has any scars, unshaven hair, tattoos, on or near the proposed treatment area. 9. Has significant history or current evidence of a medical, psychological or other disorder that, in the Investigator's opinion, would preclude enrollment in the study. 10. Has an active dermatitis or open wound in the proposed treatment area. 11. Abnormal coagulation profile including: activated partial thromboplastin time (aPTT) > ULN, international normalized ratio (INR) > ULN reference range (> 1.3), prothrombin time (PT) > ULN. 12. Has an active bacterial, fungal, or viral infection in the proposed treatment area. 13. Has known allergic reactions to any injectables. 14. Has been treated chronically in the past 3 months prior to study entry with systemic steroids or immunosuppressive drugs. 15. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs). 16. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study.
Dose and Dosing Regimen and Administration of Study Drug	At the start of the double-blind, placebo-controlled phase of the trial each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will be treated with multiple injections in a single injection session in accordance with the table below: | | RZL-012 (50mg/mL DP injectable solution) | Placebo (Injectable sterile solution) |

	<table><tr><td>**Randomized Right or left flank**</td><td>12</td><td>12</td></tr><tr><td>Single Treatment*</td><td>55 injections at 7.5mg/0.15mL per each injection point – A total of 412.5 mg/8.25 mL total dose per flank</td><td>55 injections at 0.15mL per each injection point –A total volume of 8.25 mL total dose per flank</td></tr><tr><td colspan="3">* 55 injections is the maximum number of injections. In case of smaller flanks, the number of injections may be lower.</td></tr></table> Upon completion of the double-blind phase of the study, and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo in the same manner as described in the table above. **RZL-012/placebo injections** – Treatment will cover the area of each randomized flank. A surface area of 15 cm x 6 cm will be chosen for treatment as per the temporary tattoo grid shown below. Flanks will be injected with RZL-012/placebo with the needle pointing perpendicular (90°) to skin surface. An ice pack will be placed on the injected area for pain relief immediately after injections are completed. Subjects will remain in injection position for an additional 10 minutes after dosing. The injection pattern will be based on the following grid in which the distance between rows and columns will be 1.5°cm, as seen below. In the previous clinical studies, the injection dose at each of the injection points was 5.1°mg for a low dose and 7.5°mg for a high dose with a distance of 1°cm between the injection points. In the current study, a dose of 7.5°mg is planned to be administered in each injection point with a distance of 1.5°cm between each of the points.  Needles of 27 G (1 inch needle length) will be used to allow delivery into the depth of fat tissue.
Dose Justification	The maximal dose of RZL-012 administered to subjects to date was 270 mg via 36 injections of 7.5 mg/0.15 mL per injection in a submental area, with the distance between injection sites being 1 cm. This total dose per subject and the amount given per injection site were well tolerated and not associated with any significant safety issues. To cover the flank area in the current study, the maximal dose will be increased to 412.5 mg per session via 55 injections of 7.5 mg/0.15 mL per injection

	site with the distance between injection sites of 1.5 cm. Subjects who receive a second RZL-012 dose will receive a maximal RZL-012 dose of 412.5°x°2=825 mg across 2 dosing sessions, with a 3-month interval between injection sessions. The maximal dose of RZL-012 administered to non-rodents (pigs) to date was 1,000 mg via 40 injections of 25 mg/0.5 mL per injection, with the distance between injection sites being 1-2 cm. This dose was given monthly at 4 injection sessions per pig, with every monthly injection administered to the contralateral side, and was well tolerated without any significant systemic or local side effects. Dosing pigs at 4°x°1,000 mg is equivalent to about 4°x°900 mg in humans, based on body surface area calculations. These preclinical studies provide a good margin vs anticipated human dosing both in terms of the total dose, dosing frequency (once monthly in pigs vs every 3 months in humans) and amount per injection site (25°mg in pigs vs 7.5°mg in humans).
Safety Analysis	The assessment of safety will be based on AEs which will be recorded throughout the study until the final study visit. In case of ongoing AEs at the final study visit an unscheduled visit will be scheduled for further follow-up. The assessment of safety will also include vital signs and treatment area evaluation. Treatment area evaluation includes, but is not limited to, evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus. ECG and laboratory tests including D-dimer, hematology and chemistry will be conducted at the 1 week, 4 weeks and 12 weeks visits.
Statistical Analysis	Descriptive statistics All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative by study arm. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, median, minimum and maximum for means of variables by study arm. The data will be analyzed using the SAS ® version 9.4 (SAS Institute, Cary North Carolina). Primary Endpoints: 1- Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, most updated version) terminology and presented in tables by System Organ Class (SOC) and Preferred Term (PT). 2- AE data will be listed individually and summarized by SOC and by PT within a system organ class. 3- Skin irritancy AEs related to the injection procedure will be evaluated for frequency, severity and duration by treatment group. 4- Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects that experienced Skin irritancy AEs related to the injection procedure between the study groups. 5- Laboratory tests and ECG results will be summarized in appropriate tables. Secondary Endpoints: • GAIS • Flank volume reduction from baseline to week 12, assessed by Physician Global Assessment score (GAIS). The proportion of subjects for whom an

	improvement in GAIS as indicated by a score of 0 to 6 will be compared in RZL-012-treated flanks vs placebo-treated flanks, Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects for whom an improvement in GAIS was observed between treatment groups. This will be calculated along with 95% exact confidence interval by treatment group. • Correct pre and post-treatment identification The proportion of blinded reviewers able to correctly differentiate between treated flanks will be calculated along with 95% exact confidence interval by treatment group. • Satisfaction (Yes/No questionnaire) The proportion of satisfied subjects will be calculated along with 95% exact confidence intervals for each treatment group. Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of satisfied subjects between treatment groups. • Reduction in Volume The change and relative change from baseline in Flank volume as measured by photographs at 12 weeks post-treatment will be calculated per each treatment group. The Signed rank test for two means (paired observations) will be applied for testing the statistical significance of the change and relative change from baseline at week 12 in flank volume between treatment groups.
Study Duration	Double-Blind Phase: each subject will participate in the study for 4 months, which comprises a screening period, baseline/treatment period, and follow up period. Open-Label Phase: Subjects who choose to continue with the open-label phase of the study will be followed up for an additional 3 months.
Study Centers	This will be a single center study

1.0 INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

Raziel plans to test the effects of RZL-012 injection on fat accumulation in the flank area (the lower back).

Raziel Therapeutics, Ltd. (Raziel) has discovered that a novel synthetic molecule (termed RZL-012) can help reduce fat content in humans and pigs following its injection into the subcutaneous fat. The suggested mechanism of action (MOA) of RZL-012 involves liponecrosis at the injection site, followed by a transient inflammatory response and finally by a healing process in which fibrotic tissue replaces previous fat tissue. A thermogenic effect is noted at the injection site, most likely due to a local inflammatory response. Studies in pigs show that necrosis of fat tissue at the injection site is seen as early as 24 hours after injection and is still evident 2 weeks later but is completely cleared at 12 weeks post dosing. A macrophage-mediated inflammatory response was also very prominent at 24 hours and 14 days after injection with only minimal signs of inflammation remaining at 12 weeks post dosing. Fibrosis followed a different pattern compared with liponecrosis and inflammation as it started at 14 days post dosing and became much more prominent at 12 weeks post dosing. In essence, RZL-012 enables de-novo generation of fibrotic tissue to replace excess fat tissue at selected anatomical sites.

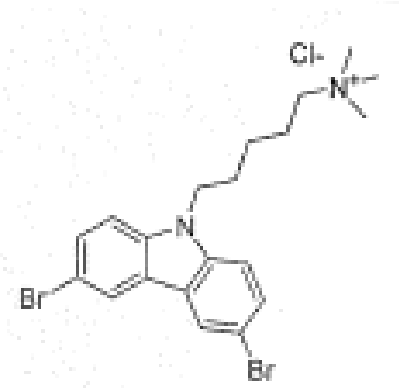
To date, Raziel has conducted several clinical studies under INDs to evaluate the safety and efficacy of RZL-012 for local fat reductions, including obesity (INDs 119941, 133324), lipomas of Dercum's Disease patients and SMF (IND 135762) and SMF reduction (IND 154260). Based on the results of these studies, Raziel concluded that the safety profile of RZL-012 is good and acceptable and the compound demonstrated efficacy in long-term reduction of local subcutaneous fat .

Based on the clinical study results received to date, Raziel continues to investigate the efficacy and safety of RZL-012 for the treatment of fat accumulation in larger parts in the body such as the flanks.

Chemically, RZL-012 is 5-(3,6-dibromo-9H-carbazol-9-yl)-N,N,N-trimethylpentan-1-aminium chloride. RZL-012 is generated by a single step reaction and the final product is >97% pure.

The molecular weight is 488 gr/mole and its structural formula, $C_{20}H_{25}Br_2ClN_2$, is illustrated in Figure 1 below.

Figure 1: Structural Formula of RZL-012



$C_{20}H_{25}Br_2ClN_2$

1.1.2. RZL-012 Formulation Development

The active ingredient RZL-012 drug substance was manufactured by Cambrex, NC, USA.

RZL-012 drug product was manufactured in Patheon (Italy) and packed and labeled at ThermoFischer, USA. The drug product is provided in vials of 240 mg/4.8 mL (50°mg/mL).

The active ingredient and formulation manufacturing and packing were in accordance with current Good Manufacturing Practices (cGMPs).

RZL-012 is provided as a sterile liquid solution suitable for injection. The quantitative composition of RZL-012 is listed in **Error! Reference source not found.** below.

Table 1 Composition of RZL-012

Component	Concentration (mg/ml)
RZL-012	50
Tween-80	100
Propylene glycol	570
Benzyl alcohol	30
Water	250

1.2. NONCLINICAL ASSESSMENTS

The RZL-012 MOA was demonstrated in pig studies following its injection into subcutaneous fat. Pigs were chosen for these studies because their SC fat resembles that of humans. RZL-012 injected into SC pig fat first caused liponecrosis at the injection site, followed by a transient inflammatory response and finally by a healing process in which fibrotic tissue replaced previous

fat tissue. The initial dose of RZL-012 to be used in clinical trials was extrapolated from the no observed adverse effect level (NOAEL) safety data obtained during animal testing.

1.2.1.1. In-vivo Efficacy Studies

A GLP study was conducted to evaluate the potential local and systemic toxicity, as well as efficacy of RZL-012, in domestic Yorkshire crossbred swine. Twenty-eight pigs received either control (0.9% Sodium Chloride for Injection) or 500 mg (20 injections of 25 mg RZL- 012) RZL-012 and observed 24 hours (3/group/sex), 14 days (2/group/sex), or 84 days (2/group/sex) post dose. Study results demonstrated that 84 days after dosing, the mean fat thickness in RZL-012-treated males was reduced approximately by 16.8% as compared to a 1.1% increase in males treated with Saline. The mean fat thickness in females treated with RZL-012 was reduced approximately by 19.1% as compared to a 3.7% increase in females treated with Saline. This study also contributed to the understanding of RZL-012 MOA. Since all injection sites (20 injection sites/pig) were quantified for necrosis, inflammation and fibrosis it was possible to demonstrate injection-related fat tissue damage followed by an acute inflammatory response which was already evident at 24 hours after injection and very prominent at 14 days. This transient inflammatory response involved mostly macrophages with little or no apparent lymphocytes seen at the injection site. Stepwise clearance of fat cell debris by surrounding macrophages was ongoing and by about 84 days after dosing the tissue was fully healed. A process of fibrosis was an active participant in this healing process, initiating already at 14 days after injection and becoming very prominent at 84 days post dose. In essence, injection of RZL-012 resulted in a long-lasting replacement of fat tissue by fibrotic tissue art the injected areas causing shrinkage of treated tissues.

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 (CNS) functions tested using FOB in rats.

The effect of RZL-012 was evaluated on respiratory functions in male Sprague Dawley rats 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 hours 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 (ECGs) 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

1.2.2.1. Single and multidose 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/rat (about 20, 40 and 80mg/kg) in Sprague-Dawley rats resulted in non-systemic effects and/or local effects at the treated skin area. Few changes observed in hematological parameters (changes in white blood cells [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 blood urea nitrogen [BUN] in males and females and increased creatinine and aspartate aminotransferase [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 (IB).

Considering skin changes as non-systemic effects and/or local effects, the NOAEL was determined at 5 mg/rat (approximately 20 mg/kg) under the test conditions and doses employed.

In the 6-month chronic rat study (Study No. G20648), 7 monthly subcutaneous administrations of RZL-012 for 6 months in Sprague-Dawley rats were well tolerated systemically in both male and female rats up to the high doses tested in both males (21.4 mg/rat) and females (14.98 mg/rat) which equated to an average mg/kg rat dose of 41.36 mg/kg in males and 49.08 mg/kg in females. Gross changes were observed at the injection sites in both sexes (males slightly worse possibly due to larger amounts of RZL-012 injected due to increased body weight compared to the females) at the end of the treatment period such as wound thickening and discoloration with inflammation, epidermal/dermal necrosis, epidermal hyperplasia or hemorrhage seen microscopically. Some of these local findings were test article (TA) related (inflammation, hyperplasia) while others were considered secondary to self-inflicted local injuries attempted by rats as a consequence of the irritation caused by test item/vehicle administration.

1.2.2.1.2. Pigs

This single dose 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 one subcutaneous injection into the subcutaneous abdominal fat on Day 0. Methods and results from this extended single dose toxicity study are described in detail in the IB.

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 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 in clinical chemistry or coagulation parameters.

In the 3-month GLP pig study, Yorkshire swine were administered 250, 500 and 1000 mg/pig of RZL-012 on Study Days 1, 29, 57 and 85. RZL-012 administration was systemically well tolerated at all dose levels. Significant local irritation was seen at injection sites (including placebo to a lesser extent) caused by the irritant properties of the compound and/or vehicle. Macroscopic findings at the injection sites included abrasions, skin scabs, and reddened skin and microscopic findings included fibrosis, inflammation, degeneration/necrosis, atrophy and regeneration of the muscularis carnosus and fibrosis and inflammation of subcutaneous tissue. The lesions were still present after an 8-week recovery period. These findings were not sufficiently severe, however to have any effects on the animals' body weight/food consumption or other endpoints with the exception of two males (1 each, mid and high dose) having a mild increase in neutrophils (increased bands) considered due to the inflammatory response noted histologically. The only other finding was cytoplasmic vacuolation in the pancreas seen at a minimal level in multiple animals in all dose groups (including controls) with a higher severity (mild; 1 male, moderate 1 male; marked 1 female) in 3/8 high dose animals. This finding was considered an exacerbation of a background finding and non-adverse. It was also not observed at the end of the post-dose period, demonstrating reversibility. Based upon the results of the study a no observable adverse effect level (NOAEL) for RZL-012 of 1000 mg/pig when injected 4 times, with an interval of 1 month between injections sessions. 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 complete healing at 84 Days.

1.2.2.2 Reproduction toxicology studies

Rat embryo-fetal Development (EFD) and Fertility and Early Embryo-fetal Development (FEED; fertility) studies have been conducted with RZL-012.

In the EFD study, structural and / or other abnormalities were evaluated in fetuses of pregnant rats injected SC with 2.5 to 20 mg/rat RZL-012 on gestations days 5, 8, 11, & 14.

Maternal parameters comprising of mean uterine weights, number of corpora lutea, implantations, and early and late resorptions/deaths and litter parameters (mean fetal weight and number of live fetuses were comparable between the placebo control group and treated groups up to the highest dose of 20 mg/rat. No test item-related changes were observed during external or fresh visceral observations of the fetuses and there were no skeletal malformations observed in any litter at any of the tested dose levels. Variants and anomalies observed in various skeletal components across RZL-012 treated groups were comparable to the vehicle control group. Based on the observations, the No Observed Adverse Effect Levels (NOAEL) for maternal toxicity is 5 mg/rat (15.3mg/kg) due to a treatment-related reduction in body weight and food consumption at $\geq$ 10 mg/rat and the NOAEL for embryo-fetal developmental toxicity is 20 mg/rat as the cesarean section and litter parameters were unaffected by treatment up to the high dose of 20 mg/rat (62.5mg/kg).

In the rat fertility study, functional effects (e.g., on libido, epididymal sperm maturation in males, effects on the estrous cycle, tubal transport, implantation and development of pre-implantation stages of the embryo in females) were evaluated in male and female rats injected SC with 2.5 to 20 mg/rat RZL-012 on Study Days 1, 8, 15 and Gestation Day 7 in the females and 1, 8, 15, 22, 29, 36 and 43 in the males.

In the males there were no treatment related mortality, clinical signs or toxicologically significant changes in body weight, body weight gain or food consumption. Mating and fertility indices, macropathology, organ weights, epididymal sperm count, sperm morphology, vas deferens sperm motility and histopathology investigations were unaffected by the treatment at any of the tested doses.

In the females there were no treatment mortality, clinical signs or toxicologically significant changes in body weight, body weight gain or food consumption during premating and gestation period. The estrous cycle length, pre-coital interval, mating and fertility indices, mean number corpora lutea and implantations, percentage of pre and post implantation losses, mean number of fetuses, gross and histopathology were unaffected by the treatment at any of the tested doses.

Subcutaneous administration of up to 20 mg/rat RZL-012 did not cause any treatment related changes on fertility and reproduction in males and females. Hence, the No Observed Adverse Effect Level (NOAEL) for males and females was considered to be 10-20 mg/rat/injection session (average mg/kg dose of 50.5 mg/kg for males and 46.2 mg/kg for females) when administered at weekly intervals

1.2.3. Clinical Studies

To date, safety data on RZL-012 has been collected from 6 clinical trials. The enrolment for an additional study for the indication of Submental Fat (SMF) is ongoing (study RZL-012-SMF-P2b-us-001) and will be completed by December 2021. Since the SMF trial includes a placebo-treatment group and is blinded, safety data is presented for the first 40 subjects injected in this study in a blinded manner, as of 19 September 2021.

All clinical trials were conducted in the US, and in all trials RZL-012 was administered via multi injections during a single injection session. Across the 6 completed clinical trials 107 subjects have received single doses of RZL-012 ranging from 5 mg to 270 mg per subject. In the ongoing RZL-012-SMF-P2b-us-001 trial, 74 subjects have been treated as of 01 November 2021. Since the trial includes 2 RZL-012 treatment groups and one placebo treatment group and subjects are randomized in a 1 to 1 to 1 ratio into one of the treatment groups, it can be estimated that an additional 48 subjects have been treated with RZL-012. Thus altogether, it is estimated that a total of 155 subjects have received single doses of RZL-012 ranging from 5 mg to 270 mg per subject.

The planned clinical study for local fat reduction in the flank aims to inject 412.5 mg of RZL-012 in one flank followed by an additional injection 3 months later to the contralateral flank. This will result in 2 sessions of injections per subject.

A summary of the clinical studies conducted by Raziel Therapeutics in presented in Table 2 below.

Table 2 Overview of Ongoing and Completed Clinical Studies

IND No. Study ID Status	Phase	Study Title	Study Design	Dosing Regimen	Study Population	Number of treated subjects and dosing
IND 119941 RZL-012-P0US-001.3 COMPLETED	0	Phase 0 Study of Three Cohorts Aiming at the Evaluation of Safety and Thermogenesis-induction of Three Escalating Doses of RZL-012 Drug Product in Overweight, Healthy Volunteers	A randomized, double-blind, vehicle-controlled, dose-escalation study with 8 subjects, 6 active and 2 control, in each of the 3 cohorts.	Cohort 1: 5 mg Cohort 2: 10 mg Cohort 3: 20 mg	Healthy, 20-40 years old, overweight by Body Mass Index (BMI) definition ($25 < BMI \leq 34.9$), adult males.	18 RZL-012 (5-20mmg) 6 Placebo
IND 133324 RZL-012-P2aUS-001.4 COMPLETED	2a	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	A randomized, double-blind, placebo-controlled, dose-escalation study with 8 subjects, 6 active and 2 control, in each of the 4 cohorts.	Cohort 1: 40 mg Cohort 2: 80 mg Cohort 3: 120 mg Cohort 4: 180 mg	Adult male subjects 20–60 years old, with $27.5 < BMI \leq 34.9$	24 RZL-012 (40-180mg) 9 Placebo

IND 135762 RZL-012-FD-P2aUS-001.7 COMPLETED	2a	An Open Label, Phase 2a Clinical Trial for the Evaluation of Safety and Efficacy of RZL-012 for the Treatment of Women with Lipedema Involving Substantial Fat above the Knee or of Women and Men with Nodular Dercum's Disease	Open-label safety and efficacy clinical trial 6 active subjects in each cohort	Cohort 1: Patients received up to 40 mg RZL-012 Cohort 2: patients received 60 mg and 80 mg RZL-012	Post-menopausal (at least 2 years) women no more than 65 years old, with lipedema involving substantial fat above the knee or nodular Dercum's disease in such women and in men 20–65 years with nodular Dercum's disease	DD: 6 RZL-012 up to 40mg Lipedema: 6 RZL-012 60-80mg
IND 135762 RZL-012-SMF-P2A-US-001.2 COMPLETED (Study report filed to IND 154260)	2a	A Single Blind, Randomized, Placebo-controlled, Phase 2a, 2-cohort Study for the Evaluation of Safety and Efficacy of RZL-012 for Submental Fat Reduction in Healthy Volunteers	A single blind, 2-cohorts (8 active vs. 4 control in cohort 1 and 10 active vs. 6 control in cohort 2), to test safety and efficacy in healthy subjects	Cohort 1: RZL-012 subjects were dosed in a range of 70-90mg, based on SMF fullness. Cohort 2: RZL-012 subjects were dosed in a range of 125-210mg, based on SMF fullness.	Men and women 18-65 years old	18 RZL-012 (70-210mg) 10 Placebo

IND 135762 RZL-012-DD-P2B-US-001.4 , COMPLETED	2b	A Double Blind, Randomized, Multi-Center, Placebo-Controlled Phase 2B Clinical Trial for the Evaluation of Efficacy and Safety of RZL-012 in Subjects having Dercum's Disease (DD) Lipomas	A double blind clinical study to test efficacy and safety in DD subjects with painful lipomas A total of 38 subjects with a randomization ratio of 1:1 were treated. At the end of the study, codes were opened and placebo subjects were offered to be treated with RZL-012. This was an open label part and 9 patients were dosed with RZL-012	At least 4 lipomas/nodules, preferably 6, and no more than 8, are injected per subject. Dosing is according to lipoma size, where the total injected dose does not exceed 240 mg per patient (48 injections of 5mg/injection).	Women and men, 18- 70 years old, diagnosed with DD having lipomas	Double blind: 20 RZL-012 (40-200mg) 18 Placebo Open label: 9 RZL-012(60-170mg)
IND 135762 RZL-012-hADMEC14-001 COMPLETED	1	An Open-Label, Single-Dose Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of subcutaneous [14C]-RZL-012 in Healthy Adult Male Subjects	This is an open-label, single-treatment session study with multi-injections to assess the absorption, metabolism, excretion, and mass balance of RZL-012. A total of 6 subjects were enrolled and were followed up for up to 28 days from injection	~72.9 mg RZL-012 containing [14C]-RZL-012 (~71.4 µCi) (1.6 mL x [45.54 mg/mL solution for SC injection)	Healthy, adult, male, 19-55 years of age	6 RZL-012 (72.9mg)

IND 154260 RZL-012-SMF-P2b-us-001 On-Going	2b	A double blind, randomized, three-arm, placebo-controlled Phase 2b study to evaluate the efficacy and safety of RZL-012 in subjects seeking submental fat reduction (RZL-012-SMF-P2bUS-001)	Phase 2b, double-blind, randomized, three-arm, placebo-controlled study. Subjects will receive a single treatment session that consists of multiple injections of RZL-012 or placebo into the submental area under the chin, after which they will be monitored for safety and efficacy over 84 days. A total of 135 subjects will be enrolled.	1. RZL low dose – dose of 163.2±20.4 mg/subject spreads over 32±4 injection points 2. RZL high dose – dose of 240±30mg/subject spread over 32±4 injection points 3. Placebo – volume of 4.8±0.6ml vehicle/subject spread over 32±4 injection points	Adult volunteers age 18 to 65 years who have consented to participate in this study	74 RZL-012 and placebo (142.8mg-270mg)

1.2.3.1.1. Protocol No. RZL-012-P0US-001.3 Status: Completed

The first-in-man clinical trial was an exploratory, randomized, double-blind, vehicle-controlled Phase 0 study, conducted under IND 119941, to evaluate the safety and thermogenesis-induction of three escalating doses of RZL-012 in overweight and obese subjects. This study also evaluated the RZL-012 pharmacokinetics from the baseline visit (Day 0) through Day 1.

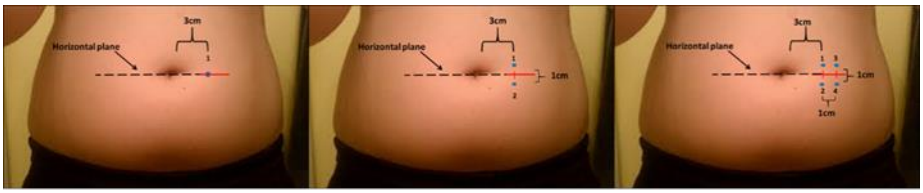
The primary objective of the study was to evaluate the overall safety of RZL-012 after subcutaneous injection and the existence of a thermogenic effect. A thermogenic effect was defined as an increase of 1 °C in the injected site when compared to the surroundings and/or the contra-lateral (non-injected site), apparent at least 28 days after injection. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera.

The secondary objective was the determination of RZL-012 pharmacodynamics. The 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 are summarized below.

The study was composed of 3 cohorts, with 8 subjects per cohort. Each subject was injected with either RZL-012 (6 subjects) or vehicle (2 subjects). This was a dose escalation study; therefore, RZL-012 was injected at doses of 5, 10, and 20 mg/subject at cohorts 1, 2, and 3, respectively. Subjects received a single treatment in multiple sites (1 - 4) of injection diagonally (45°) to the

skin surface at 3 centimeter (cm) lateral to the umbilicus lateral wall. The distance between injected sites was 1 cm (see Figure 2).

Figure 2: Injection Sites for Phase 0 Study



1st Cohort : 1 injection 2nd Cohort : 2 injections 3rd cohort : 4 injection

RZL-012-P0US-001.3 Study Results:

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 were confined to the injection site and were transient. Biopsy from the injection 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 at the surrounding of injected side (but away from the injected site).

One systemic AE involved a severe elevation of alanine transaminase (ALT) blood levels and a moderate elevation of AST blood levels 17 days following injection of the highest dose (AST 169 U/L; ALT 411 U/L) of active treatment. This elevation was transient. Resolution for AST elevated levels and reduction for ALT levels to Grade 1 according to MeDRA coding dictionary occurred 11 days following detection. ALT levels were normal on the next visit on Day 56. Other liver enzymes such as GGT and alkaline phosphatase, as well as bilirubin levels remained within normal range. There were no other systemic clinically significant AEs.

PK profile results demonstrated an association between dose and C_{max} with values of 13.11 ng/mL at the lower dose level (Cohort 1), 23.02 ng/mL at the next (double) dose level (Cohort 2) and 51.46 ng/mL at the highest (x4 of the lowest dose) dose level (Cohort 3).

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.

MRI results demonstrated a decrease over time in Subcutaneous Fat Mass (SFM) ratio (injected/non-injected side) vs baseline in most RZL-012 treated subjects of Cohort 3. This reduction was not statistically significant. 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 changes in the adipose tissue.

Raziel concludes that the potential risk-benefit balance for RZL-012 is favorable, and it is likely that higher doses of RZL-012 will generate better results.

1.2.3.1.2. Protocol No. RZL-012-P2aUS-001.4 Status: Completed

An additional clinical trial was a double-blind, randomized, placebo controlled, dose escalation Phase 2a study, conducted under IND 133324 to evaluate the safety and thermogenesis-induction of RZL-012 in overweight and obese subjects.

The primary objective of the study was the evaluation of the overall safety and preliminary efficacy of RZL-012 after subcutaneous injection. The primary endpoint for efficacy was a significant thermogenic effect, apparent at least 28 days after injection, at the injected site compared with the contra-lateral, non-injected site.

The secondary objective was the determination of RZL-012 pharmacodynamics and pharmacokinetics. The secondary efficacy endpoints included the following:

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.
4. Establishing the PK profile for RZL-012.
5. Anthropometric changes from baseline.
6. Elucidation of the histological changes that may account for the thermogenic effect by biopsy of the injection site.
7. Change from baseline in inflammatory markers and cytokines.

The study was composed of 4 cohorts. Each cohort was designed to enroll 8 subjects (6 active and 2 control). In Cohort 3, 3 subjects were injected with control vehicle and not 2 as planned due to subject's dropout. The overall number of subjects in the study was 33.

Subjects received a single treatment at multiple sites (8 - 36) of injection diagonally (45°) to the skin surface at 5 cm lateral to the umbilicus lateral wall. The distance between injected sites was 2 cm in cohorts 1 - 3 and 1 cm in Cohort 4 as seen in Figure 3.

Figure 3: Injection Sites for Phase 2A Study

RZL-012-P2aUS-001.4 Study Results:

In this study, in which significantly higher doses were tested (up to 180 mg), RZL-012 was found to be safe in all cohorts. There were no clinically significant changes in vital signs, ECG and all blood laboratory parameter. The most commonly reported AEs for which there seemed to be a causal relationship to active treatment, due to the higher incidence in the active treatment groups compared to the placebo groups, were injection site pain and injection site edema. Most

AEs were transient. There was only a single case in the highest injected dose, Cohort 4, where erythema and edema were still observed up to Day 140.

The only systemic effect due to the subcutaneous injection of RZL-012 was elevation in d-dimer values at the highest injected dose of 180 mg. However, this increase was transient, up to 3 days after injection, and non-clinically significant. Further review of coagulation parameters revealed there was no clinically significant activation of the coagulation system nor any presence of Disseminated Intravascular Coagulation (DIC). The absence of any clinical symptoms related to elevation of D-dimer supports a direct link between RZL-012 induced inflammation and elevated D-dimer levels, unrelated to venous thromboembolic disease

Biopsies taken from two injection sites revealed no damage to the skin 56 days following RZL-012 injection. Based on the histology results, the process that seemed to be dominant is fat necrosis and infiltration of macrophages into the necrotic fat tissue that resulted in a replacement of the local fat tissue by fibrotic tissue.

A decrease from baseline in SFM ratio (injected/non-injected side), as assessed by MRI, was noted in RZL-012 treated subjects of Cohorts 2 – 4 at all study time points. In addition, a dose dependent response was evident and statistically significant differences in SFM were found in RZL-012 treatment groups versus placebo. Among Cohorts 4 subjects who were monitored until 168 days post injection, a clear reduction in SFM was noticed (-14.32%). Cohort 4 subjects demonstrated the largest reduction in SFM at Day 56 (-18.10%).

There were no major changes over time and no specific trend to suggest a dose correlation response in any of the parameters of lipid profile (TC, TG, LDL, HDL, and FFA) and fasting glucose.

The PK profile of RZL-012 demonstrated dose proportionality. The maximal plasma concentration of RZL-012 was less than than 0.5 μg/mL (500 ng/mL) in all subjects and T_{max} was obtained at about 2 hours following injection.

No significant decrease in BMI or in subjects' weight values was evident in all cohorts, compared to vehicle injected subjects. There was no consistent pattern to suggest an association between inflammation markers and cytokines levels. Therefore, the inflammation reaction due to macrophage infiltration into the necrotic tissue seems to be local and without any systemic effect.

Raziel concluded that the risk benefit profile of RZL-012 as seen in the clinical trials to date, is in favor of RZL-012. RZL-012 may be useful in treating conditions in which removal of excess fat is desired (i.e., excess in SMF).

1.2.3.1.3. Protocol No. RZL-012-FD-P2aUS-001.7 Status: Completed

An additional clinical trial was an open label Phase 2a study conducted under IND 135762 to evaluate the safety and efficacy of RZL-012 for the treatment of women with lipedema involving substantial fat above the knee or of women and men with nodular Dercum's disease (DD).

The primary objective was to evaluate the overall safety of RZL-012 following injection into the subcutaneous fat in patients with lipedema or DD.

The secondary objective was to evaluate local fat reduction, its extent, duration and tissue associated changes, in response to RZL-012 treatment, utilizing minimal invasive means (ultrasound) following subcutaneous injection of RZL-012 into fatty tissue below the skin.

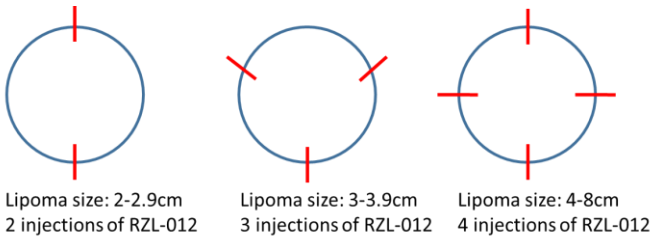
The study was composed of 2 cohorts. Cohort 1 was comprised of 6 subjects with DD and Cohort 2 was comprised of lipedema subjects having substantial fat above the knee.

Cohort 1 (Subjects with DD):

Several lipomas were injected per subject. Dosing was calculated according to the size of the nodule (diameter), reaching a maximal dose of 40 mg per subject.

Subjects received a single treatment in multiple sites (2 - 8 cm lipoma size) of injection according to the design in Figure 4.

Figure 4: Injections Diagram According to Lipomas Size



Cohort 2 (lipedema subjects with substantial fat above the knee):

The first 3 subjects received 30 mg RZL-012 in 6 injections (0.1 mL each) in one leg followed by 30 mg RZL-012 (6 injections, 0.1 mL each) in the second leg, for a total of 12 injections of 60 mg RZL-012 (see Figure 5 for injection scheme).

The last 3 subjects received 40 mg RZL-012 in 8 injections (0.1 mL each) in one leg followed by 40 mg RZL-012 (8 injections, 0.1 mL each) in the second leg, for a total of 16 injections of 80 mg RZL-012 (Figure 5).

Figure 5: Injection Scheme Lipedema Subjects

RZL-012-FD-P2aUS-001.7 Results:

Overall, 11 out of 12 subjects reported at least 1 AE, with a total of 42 reported AEs. One lipedema subject reported no AEs. Most AEs were mild or moderate in intensity.

The AEs with the highest incidence were injection site pain and headache, each of which was reported by 3 of 12 subjects (25%). Pain, contusion, sleep disorders/insomnia, and muscle spasms were each reported by 2 of 12 subjects (16.7%). All remaining AEs were reported by single subjects only.

There were 6 AEs with severe intensity, all of which were reported by a single DD subject, and included swelling (injection site, joint swelling, peripheral swelling) and pain. Following an investigation by the Principal Investigator, it was found that the subject had a tendency to scratch or rub painful lipomas and, therefore, following compound injection, lipoma scratching led to swelling and pain in the injected lipomas as well as in the surrounding areas. Most severe AEs resolved within 14 days after injection and the AE of pain resolved at 35 days. No medical intervention was required.

Measurements of lipoma size in 6 DD subjects included ultrasound measurements of height, width and length for 21 injected lipomas. Lipoma surface area was calculated by multiplying lipoma width by its length. Lipoma height was the dominant parameter when referring to its dimensions as it included aesthetic considerations and pressure application on nerves. The mean reduction in lipoma height on day 56 after injection versus baseline was -47.9±44.1% ($P<0.001$). The mean change in surface area versus baseline was 30.4±82.5% (NS).

Lipoma pain was measured by the comparative pain scale in 19 of 21 injected lipomas in 6 DD subjects (specific pain assessment per each lipoma). The mean reduction in lipoma pain on day 56 after injection versus baseline was 70±36.9% ($P<0.0001$). Sixteen (16) lipomas reported having lower pain scores compared to baseline and only 3 remained without change.

Fat thickness in 6 lipedema subjects was evaluated by averaging ultrasound measurements of fat thickness at 84 injection points (6 - 8 injection points per leg per subject). The mean reduction in fat thickness on day 56 after injection as compared to baseline was approximately 7% (NS). No improvement was noted in quality of life (QOL) measurements.

Based on the study results, Raziel concluded that RZL-012 could be beneficial in treating patients with fat disorders such as DD.

1.2.3.1.4. Protocol No. RZL-012-SMF-P2aUS-001.2 Status: Completed

An additional study was a single blind, randomized, placebo-controlled, phase 2a, 2-cohort study for the evaluation of safety and efficacy of RZL-012 for SMF reduction in healthy volunteers was conducted under IND 135762.

The primary objective was to evaluate safety following injection of RZL-012 vs. placebo injection into SMF. Skin irritancy and AEs related to injection procedure were mainly evaluated for its frequency, severity and duration. Specifically, the assessment of the following AEs was monitored: bruising, pain, induration erythema and swelling/edema.

The following secondary endpoints evaluated treatment efficacy of active treatment versus placebo subjects:

1. Reduction from baseline in SMF volume, as measured with MRI on Day 84 as compared to screening, in RZL-012 treated subjects versus placebo treated subjects.

2. Improvement of Physician' global assessment questionnaire for treatment efficacy in active versus placebo treated subjects on Day 84 visit to evaluate treatment response.

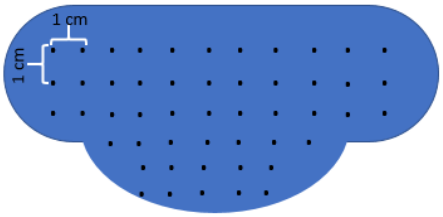
3. Improvement from baseline in subject's satisfaction rating by using validated FACE-Q questionnaire (Satisfaction of chin) on Day 84 visit to evaluate treatment response among RZL-012 treated subjects versus placebo treated subjects.

Twenty-Eight (28) subjects (12 for cohort 1 and 16 for cohort 2) were included in the study. Subjects in each cohort were injected with a different dose. Subjects in each cohort were randomized in a ratio of 2:1 of active versus placebo. A total of 28 subjects were enrolled in 2 clinical sites. Subjects were blinded to study treatment while physicians were not blinded.

Cohort 1 (N=12) – Each subject was dosed with up to 120 mg RZL-012 (depending on SMF area) or up to 2.4 mL of vehicle. Averaged injected dose was 80 mg.
Cohort 2 (N=16) – Each subject was dosed with up to 240 mg RZL-012 (depending on SMF area) or up to 4.8 mL of vehicle. Averaged injected dose was 158.5 mg.

The injection pattern in both cohorts was based on a submental area shaped grid in which the distance between rows was 1cm and distance between columns was also was 1 cm as seen in the figure below. Physicians chose two points at the edge of the 50-point pattern that were not injected (up to 48 injections) as seen in Figure 6 below:

Figure 6: Diagram of Injection Pattern



Subjects were injected with RZL-012 or vehicle perpendicularly (90°) to the skin. An ice pack was placed on the injected area for pain relief immediately after injection. Subjects had to remain seated in the injection position for an additional 10 minutes after dosing.

RZL-012-SMF-P2a-US-001 Results:

AEs were closely followed up throughout the study to determine the safety profile of RZL-012. Different scales were used to grade the severity degree of edema and erythema, pain, bruising and induration. Most of AEs were treatment related.

The most commonly reported AEs were bruising, induration, edema, pain and erythema all of which were reported with a similar incidence in the RZL-012 and placebo treatment groups. A difference was evident in the severity of some of the AEs in the RZL-012 high-dose treatment group vs. placebo with 3 reports by 3 subjects of severe edema and 2 reports by 2 subjects of severe induration in the high dose group. However, these AEs were characterized as such only within the first 24 hours of administration. The intensity then went from moderate to mild in the days following the RZL-012 injection and were completely resolved by 56 days after injection without any specific treatment or medication. Erythema, and bruising were not dose related and were mostly resolved at 14 days after injection. There were no clinically significant changes in vital signs, no deaths and no SAEs in any subjects.

Based on the objective MRI, it can be concluded that the efficacy of RZL-012 in reducing SMF in this Phase 2a study was demonstrated. This is evident by both the change in the submental depth (thickness) as well as volume. The robustness of these results is supported by the dose response that shows larger effects for the higher dose of RZL, i.e., a volume reduction of -22.2%±14.9 vs. Volume reduction of -10.6%±14.5 and -0.4%±13.9 for RZL-012 low dose and placebo, respectively.

The objective MRI assessments were supported by the Physician Impression scale. This scale which shows a more pronounced improvement at days 56 and 84 compared to day 28 may indicate that the effects of RZL-012 on SMF progress and cumulate in the weeks following the administration of the product. All besides 1 of the 18 RZL-012-treated subjects demonstrated improvement in SMF at 84 days after treatment. On the other hand, at Day 84, none of the placebo subjects demonstrated any change in their SMF.

Subjects were clearly satisfied by RZL-012 effect as indicated by the improvement of score according to Subject Face-Q Questionnaire. Subjects that were treated with RZL-012 low dose showed a 2.4-fold increase in the mean subject satisfaction. Subjects that were treated with RZL-

012 high dose showed a 2.5- fold increase in the mean subject satisfaction. Placebo subjects did not demonstrate a satisfaction on Day 84 vs. baseline.

1.2.3.1.5. Protocol No. RZL-012-DD-P2bUS-001.4 Status: Completed

Another study for DD patients, a double-blind, randomized, multi-center, placebo-controlled phase 2b clinical trial for the evaluation of efficacy and safety of RZL-012 in subjects having DD, is being conducted under IND 135762.

The primary objective is to evaluate of the efficacy of RZL-012 following injection into lipomas/nodules of DD subjects. Efficacy is determined by ultrasound assessment of the lipoma/nodule dimensions after treatment as compared to baseline assessments.

The key secondary objective is the assessment of lipoma/nodule associated pain using the Comparative Pain Scale. Safety is assessed by the frequency of AEs and by change-from-baseline values for vital signs, clinical laboratory and ECG. An exploratory objective is to follow improvement in Quality of Life by using QOL questionnaire.

A total of 38 subjects have been enrolled into the study. Subjects were randomized in a 1:1 ratio into either the RZL-012 or the placebo arm.

At least 4 lipomas/nodules, preferably 6, and no more than 8, were injected per subject. Dosing was determined according to lipoma size, where the total injected dose did exceed 240 mg per patient (48 injections of 5mg/injection). Table 3 describes the dosages according to lipoma size.

Table 3 Dosages According to Lipomas Size

Number of Subjects – Active/Placebo	20/18				
Lipoma/Nodule size – diameter (cm)	1-1.9	2-3.9	4-5.9	6-7.9	8-10
Total Dose of RZL-012 in the RZL group (mg)	10	20	40	50	60
Number of Injections	2	4	8	10	12

The injections are spread randomly on the lipoma surface with a distance between injections of at least 1 cm. Injections are given at 90° to the injected skin surface.

Once the study ends and codes are opened, 84 days after dosing, placebo-treated subjects will be offered the option of receiving treatment with RZL-012. Subjects who choose to receive treatment with RZL-012 will be followed for an additional 84 days.

RZL-012-DD-P2b-US-001.4 Results for the Double blind part:

A total of 20 subjects were injected with RZL-012 and 18 subjects were injected with placebo. The maximal dose of RZL-012 that was injected was 200mg per subject, based on painful lipomas size.

Change in Lipoma Height

Dimensions of treated lipomas were measured at baseline visit prior to injection and at each of the follow up visits by using ultrasound.

Lipoma dimensions were compared between the active and placebo treatment groups on 2 levels – (1) on the patient level and (2) by lipomas, i.e. comparison between all injected lipomas before and after injection.

The Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples was applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule height at day 84 after injection vs. baseline per patient.

The MMRM model (Mixed-effect model for repeated measures) was applied for analyzing the difference between the groups in percent reduction of lipoma/nodule height from baseline to day 84.

A total of 125 lipomas were measured at baseline in the RZL-012-treatment group and 109 lipomas in the placebo group in the double-blind phase of the study.

The by-patient analysis demonstrated an average height reduction of 11.18%±22.70 (standard deviation) in the RZL-012 treated subjects vs. an average height reduction of 15.26%±21.05 in the placebo-treated subjects (P>0.05).

The average height reduction change by lipoma analysis demonstrated a reduction of 11.22%±33.77 in the RZL-012 treated group vs. 16.28%±29.60 in the placebo group (P>0.05).

Changes in lipoma dimensions using the analysis per lipoma demonstrate a similar trend, i.e., no statistically significant changes from baseline in lipoma height were found between active and placebo lipomas. The P value was calculated by a Mixed model with repeated measure.

More than 90% of injected lipomas contained fibrotic tissue and this was the hypothesis for not demonstrating an effect on lipoma size.

Change in Lipoma Pain

Pain of each injected lipoma was assessed by a blinded subject at baseline visit prior to injection and at each of the follow-up visits by using the Comparative Pain Scale. The comparative pain scale is a scale that contains 11 grades where 0 is categorized as ‘no pain’ and 10 is categorized as ‘extreme, non tolerable pain’.

Pain was compared between the RZL-012 and placebo treatment groups on 2 levels – (1) on the patient level and (2) by lipomas, i.e. comparison between all injected lipomas before and after injection.

The Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples was applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule pain at day 84 after injection vs. baseline per patient.

The two-sample T-test for independent samples was applied for analyzing the difference between the groups in percent reduction of lipoma/nodule height from baseline to day 84.

The MMRM model (Mixed-effect model for repeated measures) was applied for analyzing the difference between the groups in percent reduction of lipoma/nodule pain from baseline to day 84.

A total of 125 lipomas were assessed for pain in baseline in the RZL-012-treatment group and 108 lipomas in the placebo group.

The all-lipoma analysis demonstrated an average pain reduction of 59.06%±40.41 in the RZL-012 treated group vs. -37.50%±49.69. The statistical significance tested by Mixed model with repeated measure generated a p value of 0.079. Calculation of statistical difference using t-test generated a p value of 0.0004.

An additional analysis calculated the proportion of subjects with at least 40% reduction in pain in each treatment group. According to the medical literature, in patients with general chronic pain, a difference in pain intensity of >30% is considered a clinically important improvement.

It was calculated that 14 out of 20 patients (70%) in the RZL-012 treated-group vs. 8 out of 18 patients (44%) in the placebo-treated group had more than 40% pain reduction. This supports the ability of RZL-012 in producing a clinical meaningful reduction in pain.

No significant change in QOL was noted according to the completed questionnaire, possibly due to the relatively small number of lipomas treated per patient.

RZL-012-DD-P2b-US-001.6 Results for the open label extension phase:

Nine (9) subjects treated with placebo in the double-blind phase of the study agreed to enter the open-label phase in which they were treated with RZL-012. A total of 65 painful lipomas were treated and followed up for pain reduction on Day 84, and 63 lipomas were followed up until Day 84 for change in dimensions.

Study results demonstrated a reduction in lipoma height of ~20% on Day 84 vs. baseline. Based on the per-patient analysis there was a mean reduction of -20.57±19.26% in lipoma height and based on the all treated lipomas analysis there was an average reduction of -21.12±29.69% in lipoma height.

No serious adverse events were reported in the study.

1.2.3.1.6. Protocol No. RZL-012-hADMEC14-001 Status: completed

A Phase 1 study which assessed the absorption, metabolism, excretion (ADME), and mass balance of 72.9mg subcutaneous injection of [14c]-RZL-012 in 6 healthy male subjects. The study was conducted under IND 135762.

The study results showed a total recovery of the administered radioactivity was approximately 85.37% (by 2 weeks after dosing), of which 2.542% and 82.83% were recovered in urine and feces, respectively, indicating that hepatobiliary excretion into the feces is the main elimination route for [14C]-RZL-012-realated material in humans, with renal elimination playing a secondary role. The PK profile of the [14C]-RZL-012 was similar to the profile shown in previous clinical studies.

[14C]-RZL-012-injected radioactivity is rapidly absorbed (T_{max} = 2hr) and widely distributed across body tissues. This is followed by a slow elimination stage with ~85% of the drug being excreted within 2 weeks. In addition, study demonstrated low/no radioactivity is remaining at one month post dose of [14C]-RZL-012 compound. Therefore, no accumulation is expected in case of once monthly or less frequent dosing regimen.

1.2.3.1.7. Protocol No. RZL-012-SMF-P2bUS-001.2 Status: Ongoing

A double blind, randomized, three-arm, placebo-controlled Phase 2b study to evaluate the efficacy and safety of RZL-012 in subjects seeking submental fat reduction, is being conducted under IND 154260.

The primary objective is to the efficacy of RZL-012 versus placebo on submental fat (SMF) reduction measured on Day 84 versus baseline using the Clinician Assessment Tool (C-CAT).

The secondary objectives are:

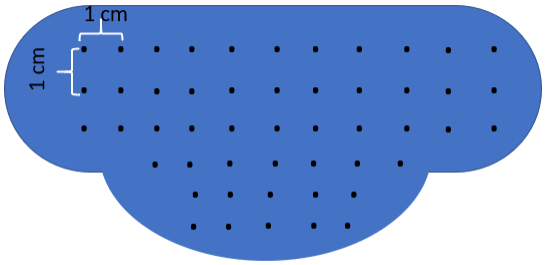
- To determine the efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using the Subject Self-Chin Assessment Tool (S-CAT);
- To assess the reduction in SMF on Day 84 versus baseline using the caliper measured submental thickness and magnetic resonance imaging (MRI);
- To assess the safety of RZL-012 in the treatment of SMF reduction.

Each subject will be randomized to either active treatment (high or low dose RZL-012) or placebo at a ratio of 1:1:1 per group and receive one of the following:

- low dose (concentration of injected solution 34 mg/mL RZL-012) of 5.1 mg/0.15 mL/injection point that results in a dose/volume of 183.6mg/5.4 mL RZL-012,
- high dose (concentration of injected solution 50 mg/mL RZL-012) of 7.5 mg/0.15 mL/injection point that results in a maximum total dose/volume of 270 mg/5.4 mL RZL-012,
- placebo of 0.15 mL/injection point that results in a total maximum volume of 4.8±0.6 mL.

The injection pattern will be based on a submental area shaped grid in which the distance between rows and columns will be 1 cm, as seen in the figure below. The Investigator will choose 32±4 sequential points on the grid that will mark the injected area according to SMF

fullness and convexity. The treatment area boundary: superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone.



Results of study RZL-012-SMF-P2bUS-001.2:

The study is blinded and still on-going.

As of 01 November 2021, total of 74 subjects have been enrolled into the study out of 155 planned subjects. Safety data that was collected for these subjects.

Overall, 97 AEs were reported in 32 out of 40 subjects (80.0%) (based on data entry as of 19 September 2021 as part of safety committee). Thirty-one subjects (77.5%) experienced AEs that were considered as related to study drug, 9 (22.5%) experienced AEs that were considered "Related to skin irritancy" and 30 (75.0%) experienced AEs that were considered "Related to injection procedure" as determined by the Investigator.

There were 5 events that were assessed as severe. Except the event of oedema, of which the outcome was not available at the time of report, all of them recovered within 28 days (1/40 = 2.5% may not have been recovered beyond 28 days).

Among 97 AEs, the most common events based on preferred term (PT) were oedema (20 events, 20 subjects), pain (15 events, 15 subjects), contusion (13 events, 13 subjects), hypoaesthesia (11 events, 11 subjects), swelling (11 events, 9 subjects), pruritus (4 events, 4 subjects), and ecchymosis (3 events, 3 subjects). Out of 97 AEs, 74 AEs (76.3%) were mild, 18 AEs (18.6%) were moderate, and 5 AEs (5.2%) were severe. Eighty AEs (82.5%) were considered as related. Eighty AEs (82.4%) were reported as recovered/resolved or recovering/resolving at the time of the report. No AEs were considered severe or life-threatening or resulted in death. No AEs were serious or resulted in discontinuation from the study.

There were 306 findings of abnormal laboratory values reported in 39 subjects after dosing. The abnormal laboratory values observed ≥ 10% (≥ 4 subjects) during the visit is as below. After dosing at Day 1, more than 10 subjects (≥ 25%) reported D-dimer, high, glucose, high, and LDH, high, whereas no subjects experienced elevated fibrinogen activity, abnormal INR, or abnormal APTT and one subject experienced slightly longer prothrombin time (12.4 sec). The ratio of number of such subjects who experienced abnormal increase at Day 1 decreased over visits and became closer to the number at screening by Day 28 except blood glucose. Of note, glucose was not necessarily measured at fasting condition.

Two (2) out of the forty injected subjects demonstrated an increase of 3-4 fold of ALT levels at day 1 and 7 post injection compared to screening levels , however these levels did not reach values that are higher than 2xULN. The other reported out-of-normal-range levels of ALT (for additional 5 subjects) were slightly elevated above normal range or were higher in screening and remained higher after injection. None of the reported subjects had elevation of 2xULN in AST values. Furthermore, there are no subjects with total serum bilirubin values or alkaline phosphatase above the normal range.

2.0 STUDY OBJECTIVES

2.1 Study Objectives

The objective of the study is to assess the safety and efficacy of RZL-012 injections into the flank area.

2.1.1 Primary Objective

The primary objective of this study is:

- To assess safety and tolerability of a single RZL-012 injection session into the flank.

2.1.2 Secondary Objective

The secondary objectives are:

- To evaluate the efficacy of RZL-012 treatment versus placebo treatment on fat reduction in the flanks
- To assess the safety of a second dose of RZL-012

2.2 Description of Study Design

This clinical trial is comprised of a double-blind, placebo-controlled phase followed by an open-label phase.

The double-blind, placebo-controlled phase of the trial will consist of a screening period, baseline visit and a 12-week post-treatment follow-up period. At the baseline visit, each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will be treated with multiple injections in a single injection session of RZL-012 or placebo. Subjects will be followed up for 12 weeks after the single treatment session.

Upon completion of the double-blind phase of the study and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo. Consenting subjects will be followed for safety and efficacy for an additional 12 weeks.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint of this study is:

- To evaluate safety following a single injection session of RZL-012 vs. placebo into the flanks. This is the first time RZL-012 is tested at a dose of 412mg per subject (highest previous dose, 270mg/subject). Lab tests, ECG, skin irritancy and AEs related to the injection procedure will be evaluated for frequency, severity and duration up to 84 days after dosing.

2.3.2 Secondary Endpoints

The secondary endpoints of this study are as follows:

- Comparison of the proportion of flanks having an improvement as indicated by a score of 0 to 6 according to the Physician Global Assessment Scale (GAIS) in RZL-012 vs placebo treated flanks.
- Comparison of the proportion of subjects who are satisfied with treatment results as indicated by a yes/no satisfaction questionnaire in RZL-012 treated flanks vs placebo treated flanks.
- Mean reduction in volume at 12 weeks post treatment vs. baseline for each of the treated flanks, as measured by 3D photographs.
- Ability of blinded reviewers to correctly identify, per patient, the flank treated with test compound (active) vs the flank treated with vehicle (placebo). Success will be defined as at least 70% correct identification vs the expected 50% correct identification based on random guessing
- .
- Evaluate safety following a second dose of RZL-012 based on AEs, laboratory tests, ECG, skin irritancy.
- Characterization of RZL-012 pharmacokinetic (PK) profile.

2.3.3 Randomization/Assignment to Study Drug

Each flank (right and left) of each study participant (12 subjects) will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will be treated with multiple injections in a single injection session of RZL-012 or placebo. Upon completion of the double-blind phase of the study, and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo.

2.4 Study Drugs

2.4.1 Test Product and Dosing

RZL-012 is a novel synthetic molecule provided as a sterile liquid solution suitable for injection.

At the start of the double-blind, placebo-controlled phase of the trial each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will be treated with multiple injections in a single injection session in accordance with Table 4 below:

Table 4 Dosing Regimen

	RZL-012 (50mg/mL DP injectable solution)	Placebo (Injectable sterile solution)
Randomized Right or left flank	12	12
Single Treatment	55 injections at 7.5mg/0.15mL per each injection point – A total of 412.5 mg/8.25 mL total dose per flank	55 injections at 0.15mL per each injection point –A total volume of 8.25 mL total dose per flank
* 55 injections are the maximum number of injections. In case of smaller flanks, the number of injections may be lower.		

Upon completion of the double-blind phase of the study and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo in the same manner as described in Table 4 above.

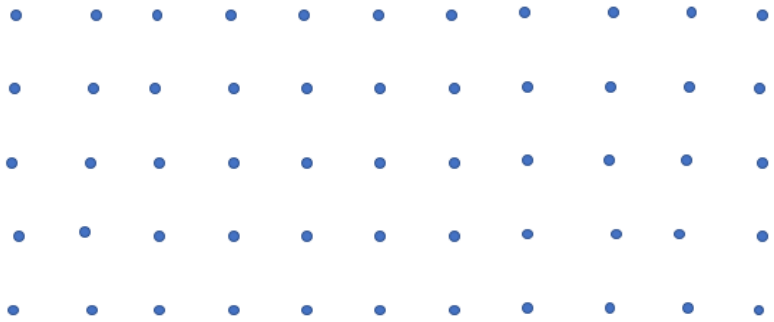
RZL-012/placebo injections –Treatment will cover the area of each randomized flank. A surface area of 15cm x6 cm will be chosen for treatment as per the temporary tattoo grid shown below.

Flanks will be injected with RZL-012/placebo with the needle pointing perpendicular (90°) to skin surface. An ice pack will be placed on the injected area for pain relief immediately after injections are completed. Subjects will remain in injection position for an additional 10 minutes after dosing.

The injection pattern will be based on the following grid in which the distance between rows and columns will be 1.5 cm, as seen below.

Injections will be conducted with a 27G needle (1 inch needle length) in order to allow direct injections into the depth of fat tissue.

Figure 7 Scheme of Injection Pattern Grid



2.4.2 Dose Rationale

The maximal dose of RZL-012 administered to subjects to date was 270 mg via 36 injections of 7.5 mg/0.15 mL per injection, with the distance between injection sites being 1 cm. This total dose per subject and the amount given per injection site were well tolerated and not associated with any significant safety issues. To cover the flank area in the current study, the maximal dose will be increased to 412.5 mg per session via 55 injections of 7.5 mg/0.15 mL per injection with the distance between injection sites of 1.5 cm. Subjects who receive a second RZL-012 dose will receive a maximal RZL-012 dose of 412.5X2=825 mg across 2 dosing sessions, at a 3-month interval between injection sessions.

The maximal dose of RZL-012 administered to non-rodents (pigs) to date was 1,000 mg via 40 injections of 25 mg/0.5 mL per injection, with the distance between injection sites being 1-2 cm. This dose was given monthly at 4 injection sessions per pig and was well tolerated without any significant systemic or local side effects. Dosing pigs at 4°x°1,000mg is equivalent to about 4°x°900 mg in humans, based on body surface area calculations. These preclinical studies provide a good margin vs anticipated human dosing both in terms of the total dose, dosing frequency (once monthly in pigs vs every 3 months in humans) and amount per injection site (25°mg in pigs vs 7.5°mg in humans).

2.4.3 Serious Adverse Events Considered Related to the Investigational Drug

AEs and serious adverse events (SAEs) will be monitored throughout the study.

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

SAEs are considered to be related to the study drug.

Subjects experiencing an SAEs will be followed for their skin condition.

SAE should be reported within 24 hours to the medical monitor.

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

- Recurring serious or severe Adverse Drug Reaction (ADR) clinically evaluated by PI as warranting study termination.
- A decision made by Sponsor/medical monitor and/or IRBEC and/or local regulatory agency to terminate the study

2.5 Concomitant Medications

2.5.1 Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until discharge assessments. All concomitant medication, 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 and changes should be updated from medical records as well.

3.0 STUDY POPULATION

The study population will include healthy volunteers age 18 to 65 years with visible and palpable fat in the flanks

3.1 Inclusion Criteria

For a subject to be eligible for this study, he or she must meet **all** of the following criteria:

1. Is a male or female subject between the ages of 18 and 65 years, inclusive.
2. Has body mass index (BMI) BMI of ≥ 22 and < 30.
3. Has clearly visible and palpable fat in the flanks
4. Has symmetrical appearance of right and left flanks
5. Agrees to maintain weight (i.e., within 5% of body weight) by not making any changes in diet.
6. Agree to avoid exposure of the treated area to sun for at least 1 month after each treatment session.
7. If female, is not pregnant or breastfeeding based on the following:
    a. agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 28 days after the last day of study drug and a negative urine pregnancy test at screening and baseline; or
    b. is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy); or
    c. is confirmed postmenopausal status (defined as either having amenorrhea for ≥ 12 consecutive months without another cause, having documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL, or having another documented medical condition (e.g., was born without a uterus))

    NOTE: The following are considered highly effective contraceptive methods: hormonal oral contraceptives, injectables, and patches; intrauterine devices; double-barrier methods (synthetic condom, diaphragm, or cervical cap used with spermicidal foam, cream, or gel); and male partner sterilization.
8. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods, e.g. condom, from study baseline until 7 days after the last day of study drug.
9. Is willing to avoid strenuous exercise for seven (7) days post treatment.
10. Is able to adhere to the visit schedule and protocol requirements and be available to complete the study.
11. Is willing and able to sign an Institutional Review Board (IRB) approved informed consent form (ICF) indicating that they are aware of the investigational nature of the study.

3.2 Exclusion Criteria

Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment:

1. Is unable to tolerate subcutaneous injections.
2. Has dysfunctional gallbladder activity (e.g., underwent cholecystectomy or cholecystitis).
3. Has any uncontrolled systemic disease that is not stabilized (i.e., cardiovascular disease, mental illness).
4. Has used anticoagulation therapies that may increase bleeding or bruising (i.e., aspirin, ibuprofen, vitamins, and herbal preparations) for seven (7) days prior to treatment.
5. Has medication or a history of coagulopathy.
6. Has a history or family history of venous thrombotic disease.
7. Has a known sensitivity to cold or has any condition with a known response to cold exposure that limits blood flow to the skin, such as cold urticaria, Raynaud's disease, or chilblains (pernio).

8. Had a non-invasive fat reduction and/or body contouring procedure in the flanks within the past 12 months.
9. Has any scars, unshaven hair, tattoos, on or near the proposed treatment area.
10. Has significant history or current evidence of a medical, psychological or other disorder that, in the Investigator's opinion, would preclude enrollment in the study.
11. Has an active dermatitis or open wound in the proposed treatment area.
12. Abnormal coagulation profile including: activated partial thromboplastin time (aPTT) > ULN, international normalized ratio (INR) > ULN reference range (> 1.3), prothrombin time (PT) > ULN.
13. Has an active bacterial, fungal, or viral infection in the proposed treatment area.
14. Has known allergic reactions to any injectables.
15. Has been treated chronically in the past three (3) months prior to study entry with systemic steroids or immunosuppressive drugs.
16. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs).
17. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study.

3.3 Subject Identification

At each site, a unique code numbers will be assigned by the Investigator to the trial subject rather than the subjects' name, 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 AE and/or other trial related data.

3.4 Removal, Replacement or Early Withdrawal of Subjects from the Assessment Not Due to Intolerable Side Effects

Subjects experiencing serious side effects will be followed until the event resolves or becomes stable.

4.0 STUDY PROCEDURES AND ASSESSMENTS

4.1 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. The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form (ICF). Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The

signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

The ICF approved by the IRB/EC will contain a description of the study's purpose, purpose, procedures, inconveniences and potential risks, and anticipated benefits. 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 ICF provided to the subjects.

After written informed consent is obtained, the subject will be assigned a screening number and will undergo the designated screening procedures listed in Appendix A. The Investigator, sub-investigator or delegate will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 3.0.

4.2 Complete Physical Examination

The Investigator (or medically qualified nominee) will perform a complete physical exam at screening and on 12 weeks visit. Additional examinations that will be performed during the screening include height and weight to determine BMI to confirm eligibility.

4.3 Medical History

A medical history will be obtained at screening. Subject's medical history should be fully documented to confirm eligibility. Medical history must include, but not limited to, past and present medical conditions, concomitant non-drug treatments, and hypersensitivity to drugs.

4.4 Vital Signs

Vital signs (systolic and diastolic sitting position blood pressure, pulse rate, respiratory rate, and body oral temperature) are to be obtained at screening to ensure compliance.

Additional vital sign measurements to assess subject's safety will be performed at baseline (Day 0) prior to treatment Week 1, Week 4, Week 8 and Week 12 visit.

4.5 ECG

ECG test is to be obtained at screening to ensure compliance. ECG will be done in triplicates.

Additional ECG will be performed on Week 1, Week 4 and Week 12 visit.

4.6 Height and Weight

Height will be reported in centimeters at screening. Body weight will be reported in kilograms (kg) at screening.

Weight measurement will be performed at screening to determine the BMI value. An additional weight measurement will be performed at baseline and at study visits on Week 4, Week 8 and

Week 12 visit to verify no significant changes in weight throughout the assessment of flank changes during the study.

4.7 Pharmacokinetics

Samples for testing of RZL-012 Pharmacokinetics will be taken from 6 subjects at the baseline visit till the following day (Day 0-1). Subjects will stay in a hotel nearby the clinic area. Blood samples (10 mL blood per sample in K_2EDTA vials, 100 mL/subject/24h) will be taken after study injection at the given time points: 0, 30, 60 min, 2h, 3h, 4h, 6h, 8h, 24h and 30h. Whole blood samples (10 mL x10 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 further. Samples (2 aliquots/subject/time point) will be sent frozen on dry ice and 2 aliquots will be retained for possible future analysis

4.8 Clinical Laboratory Evaluations – Hematology and Serum Chemistry

Screening blood samples and urine specimens for laboratory evaluation will be collected at screening to confirm eligibility. Additional blood samples will be collected at Week 1, Week 4 and Week 12 study visits for an assessment of hematology and serum chemistry.

If there are clinically significant alerts obtained at any visit, an unscheduled visit will be added for additional blood sampling.

4.8.1 Hematology

Complete blood cell count (CBC) will include a standard red blood cell (RBC), white blood cell (WBC) with differential, hemoglobin, hematocrit, platelets, D-dimer, Fibrinogen and coagulation (International normalized ratio [INR], partial thromboplastin time [PTT] and prothrombin time [PT]).

4.8.2 Serum Chemistry

Comprehensive metabolic panel will include serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, calcium, globulin (calculated), phosphorus, chloride, sodium, potassium, blood urea nitrogen (BUN)/creatinine ratio (calculated), creatinine with GFR estimated, total bilirubin, albumin, albumin/globulin ratio (calculated), total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH).

4.8.3 Pregnancy Tests

A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening and a urine pregnancy test will be administered at baseline prior to dosing. Additional serum pregnancy tests will be done at any time during the study (up to 12 weeks), if pregnancy is suspected.

4.9 2-D and 3-D Standardized Photography

Standardized photography (2-dimensional and 3- dimensional) of the flanks area will be conducted at screening in order to establish a baseline value for assessment of treatment efficacy.

Additional photography will be conducted on week 1, 4, 8 and 12 to evaluate qualitative and quantitative changes in flanks area at study visits.

The 2D photos will be used by the blinded committee to assess which of the flanks for the same subject was treated with RZL-012 or placebo by comparing each of the left and each of the right flanks images before and 12 weeks after treatment.

The 3D photos will be used to compare the images of each treated flank in screening vs. 12 weeks visit and to calculate the volumetric change before and after treatment.

4.10 Physician Global Assessment Improvement Scale (GAIS)

Investigator will assess the improvement of each flank (right and left) following treatment by comparing the photographs of the subject taken at screening versus the photographs taken at study visits on Week 4, 8 and 12 visits.

At each study visit, the Investigator will assess the improvement degree based on the following scale:

Grade		Description
0	Completely clear	No evidence of fat; 100% improvement
1	Almost clear	Very significant clearance (≥90% to <100%); only trace remain
2	Marked improvement	Significant improvement (≥75% to <90%); some evidence of fat remains
3	Moderate improvement	Intermediate between slight and marked improvement (≥50% to <75%)
4	Slight improvement	Some improvement (≥25% to <50%); significance evidence of fat remains

5	No change	Fat has not changed from baseline condition (±25%)
6	Worse	Fat is worse than at baseline evaluation by ≥25% or more

4.11 Subject's Satisfaction Questionnaire

Subject's satisfaction questionnaire (yes/no questions) will be conducted by the subjects for each of the treated flank (right and left) at study visits on Week 4, 8, and 12 to assess the subject's satisfaction with their flanks after treatment. Subjects will be asked with the following questions and answers for each question will be Yes/No:

For the right/left flank, are you satisfied with the treatment?

Would you have the treatment again in the right/left flank?

Would you recommend the treatment to a friend?

4.12 Evaluation of Response

Evaluation of response will be conducted on 12 weeks following injection of RZL-012 or placebo.

4.13 Compliance Monitoring

Compliance monitoring will include compliance assessment by site coordinator at the study visits, including but not limited to subject questioning.

5.0 SAFETY ASSESSMENTS

5.1 Collection of Adverse Events Data

Data regarding treatment-emergent AEs (TEAEs) will be collected in this study. TEAEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed while the subjects are in the study. AEs assessed by the Investigator as related to study drug and "ongoing" at discharge will be monitored by the Investigator until resolved or until the subject is deemed "lost to follow-up".

Any AEs reported by the subject or noted by the Investigator or his/her designee will be recorded on the eCRF regardless of the Investigator opinion of causality. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

The AEs reported during the trial will be graded, documented, and assessed in regards to their clinical significance and relation to study drug. Treatment area evaluation includes, but is not limited to, evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.

All abnormal changes from baseline will be collected, graded with regards to severity or clinical significance, assessed for causal relationship and recorded on the eCRF.

5.2 Complete or Targeted Physical Examination

The Investigator will perform a complete PE at screening and on 12 weeks visit.

5.3 Vital Signs

Vital signs (systolic and diastolic sitting position blood pressure, pulse rate, respiratory rate, and body oral temperature) are to be obtained at screening to ensure compliance.

Additional vital sign measurements to assess subject's safety will be performed at baseline (Day 0) prior to treatment and after treatment, and during study visits on Week 1, 4, 8 and 12.

6.0 PHARMACOKINETICS

PK measures will be assessed during this study for 6 of 12 subjects in the study. Description of the procedure is detailed in section 4.7.

7.0 EFFICACY

Efficacy measures include the following:

- Efficacy of RZL-012 versus placebo on fat reduction measured on 12 weeks visit versus baseline using the physician's GAIS and blinded committee images identification of flanks before and after treatment for each of the subject's flanks.
- Assessment of the reduction in flanks volume on 12 weeks visit compared to baseline using 3D photos.
- Assessment of flanks improvement using the subject's satisfaction questionnaire.

8.0 STUDY VISITS AND PROCEDURES

Refer to Appendix A for the Schedule of Study Procedures.

8.1 Screening (Days -28 to -1)

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form (ICF). Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The

signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned a screening number and will undergo the designated screening procedures listed in Appendix A. The Investigator, sub-investigator or delegate will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 3.0.

Screening evaluations may be performed up to 28 days in advance of dosing but must be completed at least 1 day prior to Day 0.

The following study evaluations and procedures are required to determine eligibility:

- Obtain and record a medical history, including demographics, prior medications, and concomitant medications.
- Complete physical examination
- Vital signs
- ECG
- Height and weight measurements
- Blood and serum samples for the following laboratory evaluations:
    - Hematology
    - Serum chemistry
    - Coagulation
    - Pregnancy (if applicable)
- 2D photography
- 3D photography

Subjects may be re-screened if they were screened and not dosed within 28 days. The following procedures will be performed: vital signs and weight measurements.

8.2 Baseline Evaluations (Day 0)

Following the screening visit, subjects determined to be eligible for participation in the study will undergo baseline assessments. Baseline evaluations will be performed upon admission to the clinical research unit on Day 0.

Baseline assessments include the following:

- Confirm eligibility
- Vital signs
- Weight measurement
- Concomitant medications
- Urine pregnancy test (if applicable)

Once subjects are confirmed to be eligible, each of the flanks will randomized to one of the treatment groups based on the randomization schedule.

8.3 Study Randomization

Each left and right flank will be randomized to each treatment group according to a predefined randomization scheme in a ratio of 1:1 per each subject. Assignment to treatment group will be disclosed only after subject eligibility is confirmed and immediately prior to injection treatment. The Investigator, clinical staff and the subjects will be blinded to treatment group.

8.4 Pre-dose Evaluation (Day 0)

Pre-dose assessments on Day 0 include the following:

- Vital signs
- First blood sample for PK for 6 out of 12 subjects

8.5 Drug Administration

RZL-012 and placebo will be supplied as a single treatment in multiple sites of injection (55 injections). The injection dosing regimen and technique is crucial for the therapy safety.

The following procedures prior to injection into the flanks will be applied:

1. The flank area will be cleaned with an appropriate topical antiseptic.

2. Ice/cold pack or topical local anesthesia (i.e., lidocaine cream) may be used prior to drug administration to enhance subject's comfort.

3. Injection grid pattern will be applied by pressing the grid firmly onto the clean, dry skin, with the printed grid pattern facing the skin. The grid paper backing will be thoroughly wetted with a cotton pad soaked with sterile water. After 15 seconds, the grid cover will be peeled off.

4. An area of 55 adjacent injection points will be determined following the Investigator's evaluation.

5. Syringes will be filled with 1 mL RZL-012 or placebo and the number of syringes will be compatible with the total volume of injection. Up to 9 syringes for a total volume of 8.25 mL will be used for each of the flanks.

6. All injections will be administered perpendicularly in 90 degrees, using a 1 mL Luer-lock syringe and a 27G x 1" needle, respectively.

7. The hole of the needle should be pointing into the fat layer and the injection direction should be towards the earth. An attempt to pull the plunger should be made prior to injecting to ensure no blood is coming out. If so, the plunger should be pushed down to inject 0.15 ml the medicine. The formulation is viscous; therefore, resistance is expected during injection.

8. Immediately following completion of the injections, an ice/cold pack will be applied for immediate pain relief. It will be held by the subject for at least two (2) minutes.

9. The Investigator will record the number of injections administered for each subject.

The injection pattern used will be based on the flanks area, where distance between injection rows will be 1.5 cm and distance between the injection columns will be 1.5 cm.

Each RZL-012 kit contains 2 vials that will be assigned to each subject:

- RZL-012 will be provided in vials of 240 mg/4.8 mL (50 mg/mL)

Treatment with placebo will be conducted in the same manner as above.

The calendar date and 24-hour clock time of all doses will be recorded on the CRF.

8.6 Post-dose Evaluations (Day 0) and PK blood samples

Post-dose assessments on Day 0 include the following:

- Vital signs
- Concomitant medication
- AEs

Following completion of injection treatment, an ice/cold pack will be placed on the injected area for pain relief. Subjects will remain in the injection position for an additional ten (10) minutes after injections. Six subjects will remain in the clinic up for 1 hour post dosing to collect blood for PK at time points of 30 and 60 minutes post dosing and AEs assessments. Additional blood samples for PK will be collected at: 2h, 3h, 4h, 6 and 8 hours post injection.

The other six subjects will stay up to 20 minutes post injection for medical supervisions and AEs assessment.

8.7 Study Visits (Day 1, Week 1, 4, 8, and 12)

Subjects will return to the clinical site for study visits on Day 1*,Week 1, 4 8 and 12 visits. Study visit assessments include the following:

- Vital signs
- Concomitant medication
- AEs
- Weight measurement
- Clinical laboratory tests (Weeks 1, 4, 12)
- Serum pregnancy test (in case pregnancy is suspected)
- ECG (Weeks 1, 4, 12)
- Physician's GAIS (Weeks 4, 8, 12)
- 2D and 3D Photography
- Subject's satisfaction questionnaire (Weeks 4,8, 12)
- Blinded committee to identify which of the flanks was treated with placebo and which of the flanks was treated with RZL-012 (Week 12)

*Blood sampling for PK is only relevant for 6 of 12 subjects and will be conducted on Day 1 visit after injection.

In the case of clinically significant laboratory values at any visit, the subject will return for an unscheduled visit and a repeat of hematology and serum chemistry.

8.8 Final Visit (Week 12)

Final study visit assessments include the following:

- Vital signs
- ECG
- Physical Exam
- Concomitant medication
- AEs
- Clinical laboratory tests (including serum pregnancy test, in case pregnancy is suspected)
- Weight measurement
- 2D and 3D Photography
- Physician GAIS and physician assessment
- Subject's satisfaction questionnaire
- Blinded committee identification for treated flanks

8.9 Open-Label Phase of the Study:

Upon completion of the double-blind phase of the study and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo. Consenting subjects will be followed for safety and efficacy for an additional 12 weeks.

The following visits and procedures will take place following RZL-012 injection to the placebo treated flank (there will be no screening visit in the open label part):

- Week 1 visit – vital signs, concomitant medication, ECG, labs, 2D and 3D photos, AEs.
- Week 4 visit – vitals signs, concomitant medication ,ECG, weight, labs, 2D and 3D photos, physician GAIS, subject's satisfaction questionnaire, AEs
- Week 8 visit - vitals signs, concomitant medication, weight, 2D and 3D photos, physician GAIS, subject's satisfaction questionnaire, AEs
- Week 12 visit – vitals signs, concomitant medication , physical examination, ECG, weight, labs, 2D and 3D photos, physician GAIS, subject's satisfaction questionnaire, AEs

9.0 PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the

protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered
- Death
- Significant safety event that in the opinion of the Investigator warrants discontinuation. Raziel will attempt to follow up all subjects for safety.
- Lost to follow-up after every attempt has been made to contact the subject, including sending a registered letter
- Subject withdraws consent

The Principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons.

10.0 PRODUCT SPECIFICATIONS

10.1 Description

RZL-012 is a novel synthetic molecule (termed RZL-012) that can help reduce fat content following its injection into the subcutaneous fat. Chemically, RZL-012 is 5-(3,6-dibromo-9H-carbazol-9-yl)-N,N,N-trimethylpentan-1-aminium chloride. RZL-012 is generated by a single step reaction and the final product is >97% pure.

RZL-012 is provided as a sterile liquid solution suitable for injection. RZL-012 investigational drug is intended to be administered as a single dose via multiple injections into the subcutaneous fat.

Placebo will be supplied as a vehicle control of tween-80, propylene glycol, benzyl alcohol and water.

10.2 Formulation, Packaging, and Labeling

The active ingredient RZL-012 drug substance was manufactured by Cambrex, NC, USA. RZL-012 drug product was manufactured in Patheon (Italy) and packed and labeled at ThermoFischer, USA. The drug product is provided in vials of 240 mg/4.8 mL (50 mg/mL).

The active ingredient and formulation manufacturing and packing were in accordance with cGMPs.

RZL-012 will be provided in strength of 240 mg/4.8 mL (50 mg/mL).

The placebo is a ready to use liquid to be injected into the subcutaneous fat, supplied in a 2 vials kit. Each vehicle vial contains 4.8 mL solution volume.

10.3 Receipt, Storage and Stability of RZL-012

The RZL-012 kit and placebo vehicle will be stored in the site at monitored room temperature conditions (15 - 30 degrees Celsius) protected from light.

Drug product stability has successfully reached three (3) years. 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 First In First Out (FIFO) principals.

10.4 Study Drug Administration

Each kit containing 2 vials must be kept and handled at room temperature. The vials should be manually shaken prior to injection.

1 mL Luer-lock syringes with RZL-012 solution should be filled with 27 G 1" sterile needle for a maximal dose of 412.5mg. Two vials will be used for each subject. Breached vials will not be used for another subject. Each vial must be placed back into the container. All open vials will be kept until the end of study when the Sponsor will determine if study drug should be returned or destroyed.

10.5 Ordering and Distribution of Study Drug

RZL-012 drug product was manufactured in Patheon (Italy) and packed and labeled at ThermoFischer, USA. The drug product is provided in vials of 240 mg/4.8 mL (50 mg/mL).

RZL-012 will be dispensed to the sites under monitored conditions by ThermoFischer USA.

The active ingredient and formulation manufacturing and packing were in accordance with current Good Manufacturing Practices (cGMPs).

10.6 Accountability of Study Drugs

All study drugs received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials
- Date study drug was dispensed
- Quantity dispensed
- Quantity returned
- Quantity wasted, as applicable

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

11.0 SAFETY MONITORING AND ADVERSE EVENTS

11.1 Adverse Events

Data regarding AEs will be collected in this study. AEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

AEs reported during the trial will be graded, documented, and assessed for relationship to study drug. Specifically, assessment of AEs related to skin condition and injection procedure will be closely monitored, including evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.

Definition of Adverse Events and Adverse Drug Reactions:

AEs in the eCRF will be classified according to the most recent FDA definitions and in a manner consistent with International Conference on Harmonization (ICH) guidelines. As such the following definitions will be used:

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report forms only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (**Error! Reference source not found.**).

The reporting period for AEs starts after dosing of study drug and will end at final study visit on 12 weeks visit for the double-blind phase of the study. Once codes are opened after 12 weeks visit, subjects will be offered RZL-012 in the placebo treated flanks. After dosing with a second administration, AEs will be recorded according to planned schedule in the open-label phase.

If an AE remains unresolved at discharge, the subject will be followed, at the Investigator's discretion, until resolution of the event or until the subject is deemed "lost to follow-up". AEs assessed by the Investigator as related to study drug and "ongoing" at discharge will be monitored by the Investigator until resolved or until the subject is deemed "lost to follow-up".

SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The Investigator will assess AEs for severity, relationship to IP, and as to whether the event meets one or more of the definitions of an SAE. The assessments will be recorded on the source documents and AE CRF, using the categories defined below.

Causality Category	**Description**
Un-related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event".
Related	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol, an event that has possible or probable relationship to study medication will be defined as a "Suspected Adverse Drug Reaction".

In order to classify AEs and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA.

For those AEs that are not described on the CTCAE v 5.0, such AEs will be graded on a 5-point scale (mild, moderate, severe) and reported as indicated on the CRF. Intensity of such an AE is defined as follows:

Table 5 Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 5.0)

CTCAE Grade	**Common Term**	**Description**
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Assisted Daily Living (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care

CTCAE Grade	Common Term	Description
		ADL.
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Death related to AE

11.2 Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death
- Is life-threatening
- Requires in-subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Important medical events

Although not an SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours.

11.2.1 Reporting Requirements for Serious Adverse Events

All SAEs must be reported to the Sponsor by the Investigator, study coordinator, other designated study personnel, or clinical research associate within 24 hours of notification of the SAE. To report such events, an SAE form must be completed by the Investigator and sent within 24 hours by email or fax with relevant information.

Within the 48 hours following the initial report, the Investigator must provide further information on the SAE if available. This should include a copy of the completed SAE form, and any other information that will assist the understanding of the event. Significant new information on ongoing SAEs should be provided promptly as a follow-up.

The Investigator also must report all SAEs promptly to the appropriate IRB/EC as required by the institution within 24 hours or 48 hours if on weekend/holiday.

Report SAEs by fax or email to:
Fax: +1-858-436-1401
Email: RazielSafety@pacificlinkconsulting.com/dr.patricia.walker@gmail.com

Table 6 Contact Information for SAE Reporting

Primary Contact	**Sponsor Contact**
Medical Monitor	**Study Director:**
Patricia Walker, MD, PhD	**Racheli Gueta, PhD**
Mobile: 1-805-705-5853	Mobile: 972-50-7837597
Email: dr.patricia.walker@gmail.com	Email: racheli@raziel-therapy.com

11.2.2 Reporting pregnancy

Pregnancy testing must be preformed on all women of childbearing potential prior to dosing, and all the results of all pregnancy tests are to be recorded in the eCRF's. All women must have a negative pregnancy test to be enrolled into the study. If a pregnancy test turns positive after study drug treatment, the patient will be discontinued and protocol-required procedures for study discontinuation and follow-up must be preformed. The subject will be followed to determine the outcome of the pregnancy. All women of childbearing potential should be instructed to contact the investigator if they suspect they might be pregnant (e.g. missed or late menstrual period) at any time during the study.

The investigator must notify the sponsor of any pregnancies in accordance with the SAE reporting procedures described in section 11.2.1. Note, while the pregnancy is not considered an AE or an SAE, any pregnancy complication or newborn complication will be reported as an AE or SAE if it meets the criteria. Follow-up information regarding the course of pregnancy, including perinatal and neonatal outcomes and, where applicable, offspring information must be reported on the Pregnancy Outcome eCRF.

11.2.3 Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (e.g., test results, autopsy, and discharge summary) must be obtained to supplement the SAE report form. A copy of all initial and follow-up reports must be filed with the subject's eCRF.

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

A total of 12 subjects will be included in the study. Each subject will be treated with RZL-012 in one randomized flank and placebo in the other randomized flank.

This will results in comparison of 12 active treated flanks vs. 12 placebo treated flanks.

12.2 Analysis Data Sets

Subjects who receive study treatment will be included in the safety analyses.

12.3 Endpoints Analyses

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics.

For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency, and 95% confidence interval (CI) for proportions by study arm.

For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variations (CV%), median, minimum and maximum, and 95% CI for means of variables by study arm.

The data will be analyzed using the SAS version 9.4 (SAS Institute, Cary North Carolina).

12.4 Safety

Safety data will be summarized by dose group and based on their initial dose level or treatment group (i.e., if a dose reduction occurs, they will be considered in their initial group). Descriptive statistics will be provided for actual values and change from baseline values for vital signs, blood parameters, ECG .

AE assessment and treatment area evaluation including, but not limited to evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using MedDRA™ and will be presented by body system. AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0 (**Error! Reference source not found.**).

AE data will be listed individually and summarized by SOC and by PT within a system organ class.

Skin irritancy AEs related to the injection procedure will be evaluated for frequency, severity and duration by treatment group.

Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects that experienced Skin irritancy AEs related to the injection procedure between the study groups.

Laboratory tests and ECG results will be summarized in appropriate table.

12.5 Efficacy

The secondary endpoints will be analyzed as follows:

- Physician’s GAIS

- Flank volume reduction from baseline to week 12, assessed by Physician Global Assessment score (GAIS). The proportion of flanks having an improvement as indicated by a score of 0-6 according to the Physician Global Assessment Scale (GAIS) in RZL-012 vs placebo treated flanks will be assessed.

  Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects for whom an improvement in GAIS was observed between treatment groups. Will be calculated along with 95% exact confidence interval by treatment group.

  - Correct pre and post-treatment identification

  The proportion of correctly identified photos (flank's treatment) by blinded reviewers will be calculated along with 95% exact confidence interval by treatment group.

  - Satisfaction (Yes/No question)

  The proportion of satisfied subjects will be calculated along with 95% exact confidence intervals for each treatment group. Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of satisfied subjects between treatment groups.

  - Reduction in Volume

  The change and relative change from baseline in Flank volume as measured by photographs at 12 weeks post-treatment will be calculated per each treatment group. The Signed rank test for two means (paired observations) will be applied for testing the statistical significance of the change and relative change from baseline at week 12 in flank volume between treatment groups.

13.0 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

13.1 Data Collection and Reporting

An eCRF will be completed for each subject who receives at least one dose of study drug. All entries on the eCRF must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs and vital signs) on an ongoing basis. The Investigator is required to review all entries on the eCRF and sign at appropriate time intervals.

13.2 Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current Good Clinical Practice (GCP) and Standard Operating Procedures (SOP) for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including eCRFs, source documents, etc., for review and source document verification by the clinical monitor.

All eCRFs will be 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing

procedures, and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

13.3 Audit and Inspection

The sponsor or representative may conduct audits at the trial site(s). Audits will include, but are not limited to protocol compliance, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may inspect the trial site during or after the trial. The investigator should contact the sponsor immediately if this occurs and must fully cooperate with the inspections conducted at a reasonable time in a reasonable manner.

13.4 Deviation from Clinical Trial Protocol

Deviations from the protocol are to be avoided. If a deviation occurs, the Investigator must promptly report the deviation to the study monitor.

The Investigator (or designee) will record any failure to follow the protocol because of any other medical unavoidable reason to avoid the subject's urgent risk and record a document as soon as possible stating this and the reason. It must be submitted to the sponsor and the director of the study site.

13.5 Retention of Records

The Investigator must retain all study records required by Raziel and by the applicable regulations in a secure and safe facility. The Investigator must notify Raziel of any change in the location, disposition or custody of the study files. The Investigator /institution must take measures to prevent accidental or premature destruction of essential documents, that is, documents that permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) as well as any original source documents that are electronic as required by applicable regulatory requirements.

All study records must be retained until whichever is the later day in the following: (1) At least the date of approval for the drug or (2) the date when 3 years have passed since the discontinuation or completion of the study. No records relating to this study should be disposed of without the written approval of Raziel. It is the responsibility of Raziel to inform the Investigator/institution as to when these documents no longer need to be retained.

13.6 Data Disclosure and Subject Confidentiality

Subject medical information and video recordings obtained as a result of this study is considered confidential and used only for study evaluation purposes. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by number. Medical information resulting from a subject's

participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked and secured area. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the subject, except as necessary for monitoring by the IRB, the FDA, or the study Sponsor.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor and Study Investigator.

14.0 PROTECTION OF HUMAN SUBJECTS

14.1 Basic Principles

The study will be conducted in accordance with the relevant regulatory requirements, this protocol, and ethical principles that are consisted with the GCP guideline developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This clinical trial will also be conducted in compliance with Declaration of Helsinki, protocol, Standard specified in the relevant local regulations. Prior to initiation of the study, the investigator and the sponsor should obtain approval from the IRB/IEC on this protocol and any further amendments, and the subject information and informed consent form.

Any suspected serious breaches must be immediately reported to the sponsor. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety of the subjects or the scientific value of the study.

Personnel involved in the study will be qualified by education, training, and experience to perform their respective tasks.

14.2 Institutional Review Board/Ethics Committee

The Investigator or designee agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these

documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56 (Code of Federal Regulations).

14.3 Informed Consent

The investigator is responsible for:

• Explain the subject of the study, the risks and benefits expected from participating in the study, and that the participation is voluntary so that the subject can understand.

• Obtain informed consent to participate in the trial from the subject by signing or signing the consent form and entering the date before starting the study procedure and study drugs.

• Properly answer questions from subjects at any time during the trial and if new information that can affect the subject's intention to continue the trial is obtained while the subject is participating in the trial, the information is promptly communicated to the subject.

• Give a copy of the written consent form to the study participants and keep one copy at the study site.

14.4 Subject Health Injury and Insurance

In general, if a subject is health-injured as a direct result of the investigational products, the sponsor or its contracted insurance company will pay for reasonable and necessary medical treatment for the health-injury. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor should comply with such laws or regulations. Where applicable, the sponsor will arrange for specific insurance coverage. If health damage occurred in subject participating the clinical trial due to the willful or gross negligence of investigator’s site, indemnification will be discussed based on the contract with the site. The indemnification for the health damage and the payment to subjects will be described in the ICF.

14.5 Completion of the Study

If the clinical trial is completed at the study site, the investigator will notify the director of the study site that the trial has been completed and provide an approximate summary in writing. The director of the study site will promptly notify the IRB/EC and the Sponsor in writing about the completion.

Appendix A: Schedule of Study Procedures

Table 1: Schedule of Study Procedures

Study Procedure	**Screening Day**		**Double Blind Phase**					**Open Label Phase**				
Study Day	**Day -28 through Day -1**	**Baseline Day 0 [a]**	**Day 1 [e]**	**Week 1(±2 days)**	**Week 4 (±5 days)**	**Week 8 (±5 days)**	**Week 12 (±5 days)**	**Day 0 [a]**	**Week 1(±2 days)**	**Week 4 (±5 days)**	**Week 8 (±5 days)**	**Week 12 (±5 days)/ Final visit**
Signed informed consent	X											
Eligibility criteria	X	Pre[c] X										
Medical history	X											
Physical Exam	X						X					X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X
Pregnancy ß-hCG	X											
Weight measurements	X	X			X	X	X			X	X	X
Pharmacokinetics blood samples		X	X									
Hematology and Chemistry[b]	X			X	X		X		X	X		X
ECG	X			X	X		X		X	X		X
Vital signs	X	Pre[c] X post[c]		X	X	X	X	Pre[c] X post[c]	X	X	X	X
Injection of RZL-012 or placebo		X						X				
Physician's GAIS					X	X	X			X	X	X
Subject Satisfaction questionnaire					X	X	X			X	X	X

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2D Standardized photography	X			X	X	X	X	X	X	X	X	X
3D photography	X			X	X	X	X	X	X	X	X	X
AEs[d]			X	X	X	X	X	X	X	X	X	X

a. Day 0 defined as the day of RZL-012 or placebo injection.
b. In case of clinically significant values at any visit, an unscheduled visit will be added
c. Pre/post – refers to before/after injection, respectively
d. AEs will be recorded throughout the study until the final study visit. In case of ongoing AEs at the final study visit an unscheduled visit will be scheduled for further follow-up. Treatment area will be evaluated including, but is not limited to, evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.
e. Day 1 visit is only for subjects who volunteer for PK blood samples