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

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08 March 2022

RAZIEL THERAPEUTICS LTD.

INVESTIGATIONAL NEW DRUG PROTOCOL

RZL-012

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SPONSOR:

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CONFIDENTIAL

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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
C-CAT	Clinician Chin assessment Tool
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
FOB	Functional Observational Battery
FSH	Follicle-Stimulating Hormone
GAIS	Global Aesthetics Improvement Scale
GGT	Gamma-glutamic transferase
GLP	Good Laboratory Practice

ABBREVIATION	DEFINITION
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
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
S-CAT	Subject Self-Chin Assessment Tool
SAE	Serious adverse event
SFM	Subcutaneous Fat Mass
SMF	Submental fat

ABBREVIATION	DEFINITION
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 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	Phase 2b
Study Drug	RZL-012
Study Objectives and Endpoints	• Primary Objective: • to determine 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). • Secondary Objectives: • to determine the efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using both Subject Self-Chin Assessment Tool (S-CAT) and the Clinician Assessment Tool (C-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. • Primary Endpoint: • comparison of the proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline between the RZL-012 high dose (270 mg/5.4 mL) group and the placebo group. • Secondary Endpoints: • proportion of subjects who have at least a 1-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group. • proportion of subjects who have at least a 2-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group. • reduction in SMF volume by MRI (Day 84 versus screening) in the RZL-012 groups versus placebo group. • • reduction in SMF thickness measured with caliper (Day 84 versus baseline) in the RZL-012 groups versus placebo group. • safety of RZL-012 in the treatment of SMF reduction. • Exploratory endpoints: • Physicians Global Assessment • SMF improvement using the Global Aesthetic Improvement Scale (GAIS). • Subject Global Self-Assessment • SMF improvement using the Subject Global Assessment of Change Scale. • SMF improvement using the subject's satisfaction questionnaires. • SMF improvement using Subject's impact questionnaire.
Study Design	This is a Phase 2b, double-blind, randomized, three-arm, placebo-controlled study that will consist of a screening period, baseline period, and a randomized treatment period. 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.

Following the completion of Day 84 visit of the last subject, subjects from three (3) chosen clinical sites will be followed up further twice up to a 1 year after injection to evaluate the long term safety and efficacy. The additional follow up visits will be at 6 and 12 months after injection.

For subjects from all sites that their adverse events were not resolved by Day 84, an unscheduled visit will be set 6-8 weeks after Day 84 to verify the resolution of the AE. On that visit, follow up of efficacy using C-CAT and S-CAT will also be conducted.

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.

Screening Period: Subjects will undergo screening within 28 days prior to entering into the study. Screening period will contain 2 visits, pre-screening visit to verify that subject qualifies the study based on S-CAT , C-CAT and 2D photography and another visit that will include an assessment of eligibility by measurement of SMF thickness using calipers, skin type by Fitzpatrick scale, subject's satisfaction scale related to appearance of SMF, subject impact questionnaire, and MRI. MRI will be conducted prior to the baseline visit. ECG and blood samples will also be conducted during the second screening visit.

Baseline Treatment Period: A total of 135 eligible male or female subjects will be randomized according to a predetermined randomization scheme (1:1:1 ratio) to receive a single multi-injection treatment of high dose RZL-012, low dose RZL-012, or placebo on Day 0. Subjects will be monitored for adverse events (AEs) and treatment area evaluation for 30 minutes post dose prior to discharge from the clinical trial site. Subjects will return to the site for study visits on Days 1, 7, 28, and 56 and for a final study visit on Day 84 for efficacy and safety assessments.

Subjects will be advised to continue their regular diet and physical activity during the study.

Blood samples will be collected at Day 1, 7, 28 and Day 84 study visits for assessment of hematology and serum chemistry. If there are clinically significant alerts obtained at any visit, an unscheduled visit will be added for an additional blood sampling

Safety assessments will be performed at each study visit and subjects can be released after blood sampling and study assessments are completed.

Safety assessments include vital signs, blood samples, ECG, AE assessment, and treatment area evaluation. Treatment area evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia , pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures. Concomitant medications will be recorded. An internal safety review committee will review the safety data collected during the study in a blinded manner. The committee members will include study medical monitor, Raziel's CMO and clinical director. The

	meeting will be held for every enrolled 40 subjects. Following completion of enrollment period, the committee will meet quarterly during the follow up period. The study enrollment will be suspended if either of the following occur: • Greater than 20% of subjects report a drug related grade 3 (severe) adverse event for a period duration of more than 28 days after injection. Of note severe swelling is expected and may be present for the first 24-96 hours after injection. • >1 subject with a drug related CTCAE Grade of 4 or 5 In the event of the above, the enrollment and treatment will be suspended, the safety committee will review all data to examine potential safety issue. Additional experts may be brought in to review safety data if deemed necessary by the safety committee. A safety report will be issued with the conclusions of the meeting. The recommendation of the safety committee will be documented. Potential outcomes are reinitiating enrollment with current safety practices, reinitiating study enrollment with caveats (e.g. additional precautions/limitations or safety training), stop enrollment.
Sample Size	135 subjects (45 subjects per group): 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
Study Population	Adult volunteers age 18 to 65 years who have consented to participate in this study.
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) between >22 and <40. 3. Has SMF bulge that is contiguous and fits to 32±4 injections sites according to a grid with 1 centimeter (cm) distance between injection points. 4. Has grade 3 to 4 of SMF as rated by the C-CAT. 5. Has a visible or large pocket of submental fat- according to physician global assessment. 6. Has grade 3 to 4 of SMF as rated by the S-CAT. 7. Has stable weight, with no fluctuation of >5 kg in the past 12 months. 8. 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 4 weeks after the last day of study drug and a negative serum pregnancy test (ß-hCG) at screening and negative urine pregnancy test at 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 and documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL or 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.

	9. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods as listed above in criteria 7 as well as to use a barrier method, e.g. condom , from study check-in until 7 days after the last day of study drug. 10. Is willing to avoid strenuous exercise for seven (7) days post treatment. 11. Is able to adhere to the visit schedule and protocol requirements and be available to complete the study. 12. 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 any uncontrolled systemic disease that is not stabilized (i.e., cardiovascular disease, mental illness). 4. Has had treatment with botulinum toxin injections in the neck or chin area within nine (9) months prior to screening. 5. 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. 6. Has skin laxity (i.e., elastosis, skin crepiness, skin redundancy, skin draping, vertical and/or horizontal skin bands and folds, blunting of cervical mental angle, loss of opposition of skin to underlying neck structures due to skin laxity) that could obscure the evaluation and treatment of SMF. 7. Has any scars, unshaven hair, tattoos, facial hair or jewelry on or near the proposed treatment area. 8. Has presence of structures or confounding factors that may interfere with assessing SMF such as but not limited to enlarged submandibular salivary and/or parotid glands, micrognanthia, chin implant, soft tissue volume augmentation of chin and/or jawline, pronounced platysmal bands and deep necklace lines or presence of facial jowls that could obscure the evaluation of SMF. 9. Has a fat bulge under the chin that is too large to be adequately treated by 32+/-4 contiguous injections on a 1cm grid . 10. Has a fat bulge under the chin that is of an insufficient volume to allow 28 injections within a contiguous 1 cm grid. 11. 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. 12. Has an active dermatitis or open wound in the proposed treatment area. 13. Abnormal coagulation profile including: activated partial thromboplastin time (aPTT) > ULN, international normalized ratio (INR) > ULN reference range (> 1.3), prothrombin time (PT) > ULN 14. Has D-dimer value >0.64mg/L in screening visit 15. Has an active bacterial, fungal, or viral infection in the proposed treatment area. 16. Has a pre-existing skin condition in the submental region that, at the Investigator's discretion, may confound evaluation or analysis. 17. Has previously had treatments or surgery in the submentum, such as but not limited to, focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate, or neck lift. 18. Has pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia, or facial nerve palsy. 19. Has Dercum's Disease. 20. Has allergic reactions to injectables.

<table>
<tr><td></td><td>
21. Has any pre-existing medical condition other than increased SMF that, at the Investigator's discretion, may result in increased submental fullness, such as but not limited to, thyroid enlargement, goiter, cervical lymphadenopathy, etc.
22. Has a planned fat reduction procedure of any variety to the submental region for the duration of the study.
23. Has medication or a history of coagulopathy.
24. Has a history or family history of venous thrombotic disease.
25. Has been treated chronically at least three (3) months prior to study entry with systemic steroids or immunosuppressive drugs.
26. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs).
27. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study.
28. Has claustrophobia or an MRI incompatible device or implant.
</td></tr>
<tr><td>Dosage and Administration of Study Drug</td><td>
All subjects will receive a single multi-injection session of RZL-012 or placebo in accordance with the table below:
<table>
<tr><td></td><td colspan="3">N=135</td></tr>
<tr><td></td><td>RZL-012 High dose (50mg/mL)</td><td>RZL-012 Low dose (34mg/mL)</td><td>Placebo</td></tr>
<tr><td>Number of subjects (N)</td><td>45</td><td>45</td><td>45</td></tr>
<tr><td>Maximum RZL-012 dose (mg)/volume (mL)</td><td>270mg/5.4 mL</td><td>183.6 mg/5.4 mL</td><td>0mg/5.4±0.6mL</td></tr>
<tr><td>RZL-012 Dose (mg)/volume (mL) per single injection</td><td>7.5mg/0.15mL</td><td>5.1mg/0.15mL</td><td>0mg/0.15mL</td></tr>
<tr><td>Number of Injections per subject</td><td colspan="3">32±4, maximum of 36</td></tr>
</table>
Subjects treated with RZL-012 will undergo a single treatment session with 32±4 injections. The maximal number of injections will be 36 with maximal doses of 183.6 mg and 270 mg for the low and high doses, respectively. Each injection point will be dosed with 5.1 mg RZL-012 for the low dose or 7.5 mg for the high dose in a volume of 0.15 mL/injection site. Placebo (vehicle) subjects will be injected with a 0.15 mL vehicle per each injection site. The maximal injection volume for all groups will be up to 5.4 mL.
Subjects will be injected with RZL-012 or placebo perpendicularly (90°) to the skin. An ice pack will be placed on the injected area for pain relief immediately after injection. Subjects will remain seated in the injection position for an additional 10 minutes after dosing.
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.
</td></tr>
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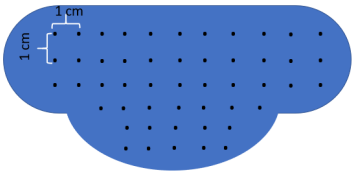
	
Safety Analysis	AEs will be collected and reviewed to evaluate the safety and tolerability of RZL-012. AE collection will begin after dosing and will end at discharge assessments on Day 84. AEs may be either spontaneously reported or elicited during questioning and examination of a subject. AE information will be elicited at appropriate intervals by indirect questioning using a non-leading question. Other safety measures will include vital sign measurements, ECG, blood samples, and treatment area evaluation. Treatment area evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, , pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures. Concomitant medications will be recorded. An internal safety review committee will review the safety data collected during the study in a blinded manner. The meeting will be held for every enrolled 40 subjects. Following completion of enrollment period, the committee will meet quarterly during the follow up period.

Statistical Analysis	A sample size of 135 subjects will be included in the study, divided into three (3) groups: RZL-012 low dose (up to 183.6 mg/5.4 mL), RZL-012 high dose (up to 270 mg/5.4 mL) and placebo (up to 5.4 mL), with 45 subjects in each group. For the primary endpoint (proportion of high-dose group subjects who have at least a 1-grade improvement from baseline to day 84 on the C-CAT scale), the assumed true rates are 70% in the RZL-012 high dose group and 35% in the placebo group (a difference of 35 percentage points). Based on the use of a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance, 41 subjects per group are required at 90% power. In order to account for a dropout rate of up to ~9%, the planned sample size is 45 subjects per group, for a total sample size of 135 subjects. Secondary endpoints (improvement in 1 point in S-CAT and C-CAT, improvement in 2 points in both S-CAT and C-CAT) will be tested using a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance. If the primary analysis is not statistically significant, then the results of the secondary analysis will be exploratory rather than confirmatory. All secondary endpoints will be tested using a two-sided test at the alpha=0.05 level of significance. All other secondary endpoints will be tested using a two-sided test at the alpha=0.05 level of significance. 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). For the primary endpoint analysis, Pearson's chi-square test will test the statistical significance of the difference in the proportion of responding subjects between the high dose RZL-012 group and the placebo group. A responder is defined as a subject who has at least a 1-grade improvement between Day 84 and baseline on the C-CAT.
Study Duration	It is planned that each subject will participate in the study for four (4) months, which comprises a screening period, baseline/treatment period, and follow up period. In 3 chosen clinical sites, there will be additional follow up of subjects for maximum 1 year period.
Study Centers	Up to twelve (12) centers

1.0 INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

Submental fat (SMF) can represents an aesthetic problem in males and females. Although localized fat deposits are present in many parts of the body, SMF is particularly noticeable due to its location. Until recently, treatments of SMF have been limited to invasive, surgical procedures such as liposuction or fat excision and even complete neck reconstruction. Because surgery is associated with the risks of anesthesia, infection, bleeding, bruising, and scarring, as well as the possibility of poor outcome, discomfort, and the prolonged "down time" for the patient, there is a large demand for nonsurgical alternatives (1-3). The submental area represents an ideal anatomical area for an injectable treatment for fat reduction. Recently, several treatments were developed and approved as 'non-invasive' treatments for fat reduction, i.e., freezing (medical device) and injection into the subcutaneous fat. Kybella, a drug which is based on sodium deoxycholate, was approved as an injectable treatment for SMF. However, due to repeated treatments (up to 6 treatments) and adverse events (AEs) such as swelling and bruising after every treatment, physicians and patients are still searching for additional alternatives for SMF reduction.

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.

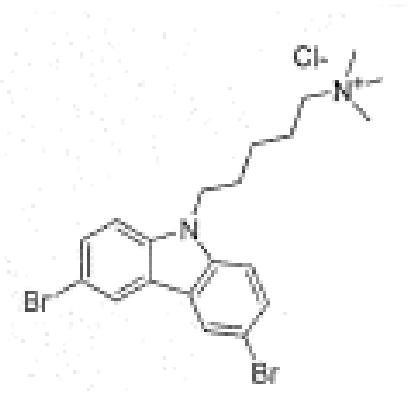
To date, Raziel has conducted several clinical studies under INDs to evaluate the safety and efficacy of RZL-012 for local fat reductions, including obesity (INDs 11941, 133324) and lipomas of Dercum's Disease subjects (IND 135762). Based on the results of these studies, Raziel concluded that the safety profile of RZL-012 is good and acceptable and the compound demonstrated efficacy in long-term reduction of local subcutaneous fat mass.

Based on the clinical study results received to date, Raziel continues to investigate the efficacy and safety of RZL-012 for the treatment of SMF in a larger clinical population and conducted in a more controlled manner.

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) and 163mg/4.8 mL (34 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 Table 1 below.

Table 1: Composition of RZL-012

Component	Concentration (mg/ml)
RZL-012	50 and 34
Tween-80	100
Propylene glycol	570

Component	Concentration (mg/ml)
Benzyl alcohol	30
Water	250

1.2. NONCLINICAL ASSESSMENTS

1.2.1. Pharmacology

Pig studies concluded that the RZL-012 MOA following injection into the subcutaneous fat 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. The 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

The effect of RZL-012 injection Several nonclinical studies in pigs, in which the subcutaneous fat tissues resembles that of humans, were conducted to prove the efficacy of RZL-012 following its injection to the subcutaneous fat. Each single administration was based on multi injections of RZL-012.

1. A non-GLP study where four domestic pigs (2 male/2 female) were injected with either a single dose of 350 mg (14 injections of 25 mg RZL-012) or vehicle. Study results demonstrated that body weight, body temperature, and physical examinations were all normal throughout the 14-day monitoring period. There seemed to be no clear difference in fat tissue depth regarding gender or treatments provided.

2. A non-GLP study was conducted to assess the influence of RZL-012 for the reduction of adipose tissue in two male pigs. One (1) was injected with a single dose of 200 mg (8 injections of 25 mg RZL-012) RZL-012 and the other with vehicle. Both pigs were injected in their right side and the left side of each pig was left untreated. Study results demonstrated that 28 days after treatment, no local injection site reactions were observed. Body weight, body temperature, and physical examinations were all normal throughout the monitoring period. No pathological findings were reported at necropsy. Post-treatment, measurements of the subcutaneous fat depth of the RZL-012-treated side was markedly lower (~30%) than that of the untreated side. This observation was not evident in the vehicle- treated pig.

3. 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 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 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

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

1.2.2.1. Extended Single Dose Toxicity Studies

1.2.2.1.1. Rats

Single subcutaneous administration of test item RZL-012 at the doses of 5, 10, and 20 mg/kg in Sprague-Dawley rats resulted in non-systemic effects and/or local effects at the treated skin area. Few changes observed in 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.

1.2.2.1.2. Pigs

This study was conducted to evaluate the potential local and systemic toxicity as well as efficacy of the test article, RZL-012 (50 mg/mL), in domestic Yorkshire crossbred swine following subcutaneous injection into the subcutaneous abdominal fat on Day 0. Methods and results from the extended single dose toxicity in pigs study are described in 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.

1.2.3. Additional Nonclinical Studies

- Secondary pharmacology
- ADME-Toxicology study: Establishing pharmacokinetic (PK) parameters, absorption, distribution and metabolism and excretion
- RZL-012 genotoxicity (in-vitro and in-vivo)

- Absorption studies in rats and pigs
- MOA – in vitro studies

Methods and results from these safety studies are described in the IB.

1.2.4. Clinical Studies

RZL-012 has been tested in several clinical trials. A total of 92 subjects were exposed to RZL-012 at single doses of up to 240 mg. The currently planned clinical trial is the second trial to assess the potential efficacy of RZL-012 in reducing SMF volume.

Five studies have been completed and efficacy analysis was completed to 4 out of the 5 studies.

Safety analysis of all studies demonstrated that 91/92 subjects has adverse events (AEs). None of the studies was reported with serious AEs. Most of AEs were mild to moderate and were associated with local injection site reactions. Only 10 subjects were reported with severe AEs (7% of the reported events).

Table 2: Overview of Ongoing and Completed Clinical Studies

Study ID STATUS	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population
RZL-012-P0US-001.3 **COMPLETED**	0	USA	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 that will enroll 8 subjects, 6 active and 2 control, in each of 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 ≤ 34.9), adult males.
RZL-012-P2aUS-001.4 **COMPLETED**	2a	USA	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, consecutive 4 cohort, dose escalation clinical trial	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 ≤ 34.9

Study ID STATUS	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population
RZL-012-FD-P2aUS-001.7 **COMPLETED**	2a	USA	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	Cohort 1 DD: Subjects received up to 40 mg RZL-012 Cohort 2 Lipedema: Each 3 subjects received 60 mg or 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
RZL-012-SMF-P2aUS-001.2 **COMPLETED**	2a	USA	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 clinical study to test safety and efficacy in healthy subjects	Cohort 1: 8 active (RZL-012) and 4 placebo subjects were injected with up to 120mg/2.4mL, based on SMF fullness. Cohort 2: 10 active and 6 placebo subjects were injected with up to 240mg/4.8mL, based on SMF fullness.	Men and women 18-65 years old
RZL-012-DD-P2bUS-001.4 **COMPLETED. Pending efficacy analysis.**	2b	USA	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	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

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

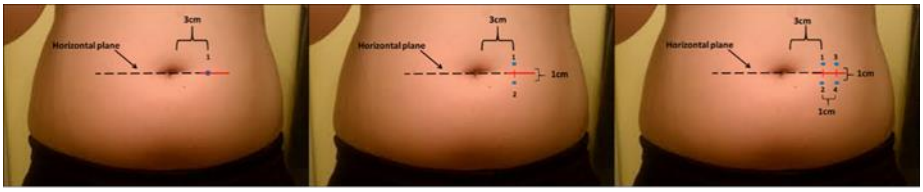
The first-in-man clinical trial was an exploratory, randomized, double-blind, vehicle-controlled Phase 0 study, conducted under IND 119941, to evaluate the safety and thermogenesis-induction of three escalating doses of RZL-012 in overweight and obese subjects. This study also evaluated the RZL-012 pharmacokinetics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



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 clinically significant 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. 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.

1.2.4.1.2. 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:

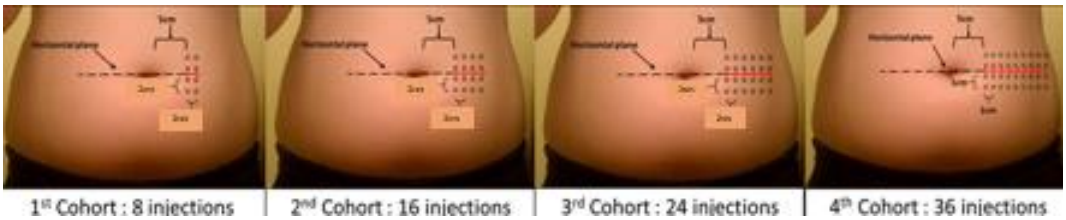
1. Duration of the thermogenic effect, defined as a net-delta ≥ 1.
2. Local reduction in fat mass as determined by MRI.
3. Clinical laboratory changes from baseline.
4. Establishing the PK profile for RZL-012.
5. Anthropometric changes from baseline.

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).

1.2.4.1.3. 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.

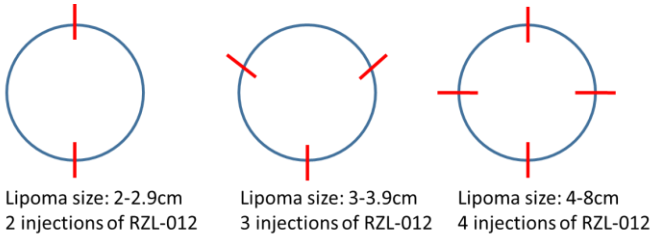
The study was composed of 2 cohorts. Cohort 1 was comprised of 6 subjects with DD and Cohort 2 was comprised of lipedema subjects having substantial fat above the knee.

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.

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

An additional study was of 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.

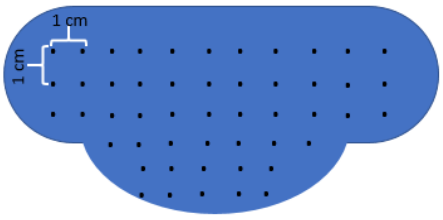
3. Improvement from baseline in subject's satisfaction rating by using validated FACE-Q questionnaire (Satisfaction of chin) on Day 84 visit to evaluate treatment response among RZL-012 treated subjects versus placebo treated subjects.

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.

1.2.4.1.5. Protocol No. RZL-012-DD-P2bUS-001.4 Status: On-going

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:

All 38 subjects were enrolled and treated in accordance with the treatment arm to which they were randomized. Study results are pending.

Safety results to date have demonstrated a tolerable and good safety profile. There were no systemic or serious AEs were reported.

2.0 STUDY OBJECTIVES

2.1 Study Objectives

Raziel continues to investigate the efficacy and safety of RZL-012 for the treatment of SMF in a larger clinical population and conducted in a more controlled manner.

2.1.1 Primary Objective

The primary objective of this study is as follows:

- to determine the efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using the Clinician Chin Assessment Tool (C-CAT).

2.1.2 Secondary Objectives

The secondary objectives of this study are as follows:

- to determine the efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using both Subject Self-Chin Assessment Tool (S-CAT) and the Clinician Assessment Tool (C-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.

2.2 Description of Study Design

This is a Phase 2b, double-blind, randomized, three-arm, placebo-controlled study that will consist of a screening period, baseline period, and a randomized treatment period.

Subjects will receive a single treatment session that consists of multiple injections of RZL-012 or placebo (tween-80, propylene glycol, benzyl alcohol, and water) into the submental area under the chin, after which they will be monitored for safety and efficacy over 84 days.

Following the Day 84 visit of the last subject, subjects from three (3) chosen clinical sites will be followed up further twice up to a 1 year after injection to evaluate the long term safety and efficacy. The additional follow up visits will be at 6 and 12 months after injection.

For subjects from all sites that their adverse events were not resolved by Day 84, an unscheduled visit will be set 6-8 weeks after Day 84 to verify the resolution of the AE. On that visit, follow up of efficacy using C-CAT and S-CAT will also be conducted.

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 163.2±20.4 mg/4.8±0.6 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 240±30 mg/4.8±0.6 mL RZL-012,
- placebo of 0.15 mL/injection point that results in a total maximum volume of 4.8±0.6 mL.

Screening period: Subjects will undergo screening within 28 days prior to entering into the study.

Screening period will contain 2 visits, pre-screening visit to verify that subject qualifies the study based on S-CAT , C-CAT and 2D photography and another visit that will include an assessment of eligibility by measurement of SMF thickness using calipers, skin type by Fitzpatrick scale, subject's satisfaction scale related to appearance of SMF, subject impact questionnaire, and MRI. MRI will be conducted prior to the baseline visit. ECG and blood samples will also be conducted during the second screening visit.

Baseline treatment period: A total of 135 eligible male or female subjects will be randomized according to a predetermined randomization scheme (1:1:1 ratio) to receive a single multi-injection treatment of high dose RZL-012, low dose RZL-012, or placebo on Day 0. Subjects will be monitored for AEs and treatment area evaluation for 30 minutes post dose prior to discharge from the clinical trial site. Subjects will return to the site for study visits on Days 1, 7, 28, and 56 and for a final study visit on Day 84 for efficacy and safety assessments.

Subjects will be advised to continue their regular diet and physical activity during the study.

Blood samples will be collected at Day 1, 7, 28 and Day 84 study visits for assessment of hematology and serum chemistry. If there are clinically significant alerts obtained at any visit, , an unscheduled visit will be added foradditional blood sampling.

Safety assessments will be performed at each study visit and subjects can be released after blood sampling and study assessments are completed.

Safety assessments include vital signs, ECG, blood samples, AE assessment, and treatment area evaluation. Treatment area evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia , pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures .. Concomitant medications will be recorded. An internal safety review committee will review the safety data collected during the study in a blinded manner. The committee members will include study medical monitor, Raziel's CMO and clinical director. The meeting will be held for every 40 subjects enrolled. Following completion of enrollment period, the committee will meet quarterly during the follow up period.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint of this study is as follows:

- comparison of the proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline between the RZL-012 high dose (270 mg/5.4 mL) group and the placebo group.

2.3.2 Secondary Endpoints

The secondary endpoints of this study are as follows:

- Proportion of subjects who have at least a 1-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group.
- Proportion of subjects who have at least a 2-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group.
- Reduction in SMF volume by MRI (Day 84 versus screening) in the RZL-012 groups versus placebo group.
- Reduction in SMF thickness measured with caliper (Day 84 versus baseline) in the RZL-012 groups versus placebo group.Safety assessment of RZL-012 in the treatment of SMF reduction.
- safety of RZL-012 in the treatment of SMF reduction.

2.3.3 Exploratory Endpoints

The exploratory endpoints of this study are as follows:

- SMF improvement using the Global Aesthetic Improvement Scale (GAIS).
- SMF improvement using the physician Global Assessment of Change Scale.
- SMF improvement using the Subjects Global Self-Assessment of Change Scale
- SMF improvement using the Subject Global Assessment of Change Scale.
- SMF improvement using the subject's satisfaction questionnaires.
- SMF improvement using Subject's impact questionnaire.

2.3.4 Randomization/Assignment to Study Drug

A total of 135 eligible male or female subjects (45 subjects per group) will be randomized according to a predetermined randomization scheme (1:1:1 ratio) to receive a single multi-injection treatment of high dose RZL-012, low dose RZL-012, or placebo. Each subject will be randomized to receive one of the following:

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.

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.

All subjects will receive a single treatment of RZL-012 or placebo in multiple injections in accordance with the treatment cohort schedule as shown in Table 4 below:

Table 4: Dosing Regimen

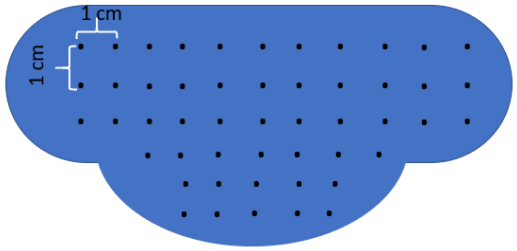
	N=135		
	RZL-012 High dose (50mg/mL)	**RZL-012 Low dose (34mg/mL)**	**Placebo**
Number of subjects (N)	45	45	45
Maximum RZL-012 dose (mg)/volume (mL)	270mg/5.4 mL	183.6 mg/5.4 mL	0mg/5.4±0.6mL
RZL-012 Dose (mg)/volume (mL) per single injection	7.5mg/0.15mL	5.1mg/0.15mL	0mg/0.15mL
Number of Injections per subject	32±4, maximum of 36		

Subjects treated with RZL-012 will undergo a single treatment session with 32±4 injections. The maximal number of injections will be 36 with maximal doses of 183.6 mg and 270 mg for the low and high doses, respectively. Each injection point will be dosed with 5.1 mg RZL-012 for the low dose or 7.5 mg for the high dose in a volume of 0.15 mL/injection site. Placebo subjects will be injected with a 0.15 mL placebo per each injection site. The maximal injection volume for all groups will be up to 5.4 mL.

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

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 Figure 7 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.

Figure 7: Scheme of Injection Pattern Grid



An internal safety review committee will review the safety data collected during the study in a blinded manner. The committee members will include study medical monitor, Raziel's CMO and clinical director. The meeting will be held for every enrolled 40 subjects. Following completion of enrollment period, the committee will meet every quarterly during the follow up period.

2.4.2 Dose Rationale

The maximal RZL-012 dose tested in the SMF phase 2a study was 210 mg, which is 87.5% of the NOAEL. No serious AEs were associated with this dose per injection site (5mg, 0.1mL), with the distance maintained between injection sites (1cm) or with the maximal overall dose. A distance of 1 cm will allow a good distribution RZL-012 into the submental area.

The averaged doses that were injected during phase 2a study were based on injection of 32 injections points on the grid that were spread with a distance of 1cm between injection columns and rows of the SMF pattern. Therefore, in the current phase 2b study, an area which includes 32±4 injection points on the submental pattern grid was chosen.

For this study, two (2) doses have been chosen where the local injection volume is increased to 0.15 mL per injection site with a dose of 5.1 mg per injection site for RZL-012 low dose. Therefore, a maximal injection volume and dose will result in a maximal dose of 183.6 mg/5.4 mL into SMF area.

To increase the potential to demonstrate efficacy, a higher RZL-012 dose of RZL will also be assessed with a dose of 7.5 mg per injection site. Therefore, a maximal injection volume and dose for RZL-012 high dose will result in a maximal dose of 270 mg/5.4 mL into SMF area.

An increase from 240 mg which was determined as the NOAEL is justified based on available preclinical and clinical safety data of RZL-012.

Based on Kyebella's studies, injections up to 10 mL into the SMF area are acceptable.

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 be male or female adult healthy volunteers age 18 to 65 years who have consented to participate in this study.

3.1 Inclusion Criteria

1. For a subject to be eligible for this study, he or she must meet **all** of the following criteria: Is a male or female subject between the ages of 18 and 65 years, inclusive.
2. Has body mass index (BMI) between >22 and <40.
3. Has SMF bulge that is contiguous and fits to 32±4 injections sites according to a grid with 1 centimeter (cm) distance between injection points.
4. Has grade 3 to 4 of SMF as rated by the C-CAT.
5. Has a visible or large pocket of submental fat- according to physician global assessment.
6. Has grade 3 to 4 of SMF as rated by the S-CAT.
7. Has stable weight, with no fluctuation of >5 kg in the past 12 months.
8. 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 4 weeks after the last day of study drug and a negative serum pregnancy test (ß-hCG) at screening and negative urine pregnancy test at 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 and documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL or 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.

9. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods e.g., condom , from study check-in until 7 days after the last day of study drug.
10. Is willing to avoid strenuous exercise for seven (7) days post treatment.
11. Is able to adhere to the visit schedule and protocol requirements and be available to complete the study.
12. 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 had treatment with botulinum toxin injections in the neck or chin area within nine (9) months prior to screening.

5. 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.

6. Has skin laxity (i.e., elastosis, skin crepiness, skin redundancy, skin draping, vertical and/or horizontal skin bands and folds, blunting of cervical mental angle, loss of opposition of skin to underlying neck structures due to skin laxity) that could obscure the evaluation and treatment of SMF.

7. Has any scars, unshaven hair, tattoos, facial hair or jewelry on or near the proposed treatment area.

8. Has presence of structures or confounding factors that may interfere with assessing SMF such as but not limited to enlarged submandibular salivary and/or parotid glands, micrognanthia, chin implant, soft tissue volume augmentation of chin and/or jawline, pronounced platysmal bands and deep necklace lines or presence of facial jowls that could obscure the evaluation of SMF.

9. Has a fat bulge under the chin that is too large to be adequately treated by 32+/-4 contiguous injections on a 1cm grid .

10. Has a fat bulge under the chin that is of an insufficient volume to allow 28 injections within a contiguous 1 cm grid.

11. 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.

12. Has an active dermatitis or open wound in the proposed treatment area.

13. Has abnormal coagulation tests (PT, PTT)

14. Has D-dimer value >0.64mg/L in screening visit

15. Has an active bacterial, fungal, or viral infection in the proposed treatment area.

16. Has a pre-existing skin condition in the submental region that, at the Investigator's discretion, may confound evaluation or analysis.

17. Has previously had treatments or surgery in the submentum, such as but not limited to, focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate, or neck lift.

18. Has pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia, or facial nerve palsy.

19. Has Dercum's Disease

20. Has allergic reactions to injectables.

21. Has any pre-existing medical condition other than increased SMF that, at the Investigator's discretion, may result in increased submental fullness, such as but not limited to, thyroid enlargement, goiter, cervical lymphadenopathy, etc.

22. Has a planned fat reduction procedure of any variety to the submental region for the duration of the study.

23. Has medication or a history of coagulopathy.

24. Has a history or family history of venous thrombotic disease.

25. Has been treated chronically at least three (3) months prior to study entry with systemic steroids or immunosuppressive drugs.

26. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs).

27. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study.

28. Has claustrophobia or an MRI incompatible device or implant.

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 withdrawn from the study, but will be followed until the event resolves or becomes stable. If a subject is withdrawn or removed from the study due to serious side effects, the subject will not be replaced.

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 Day 84. Additional examinations that will be performed during the screening include height and weight to determine BMI to confirm eligibility.

A skin type score using Fitzpatrick Skin Type will be performed. Skin type will be assessed prior to injection in order to determine skin sensitivity to treatment. The Fitzpatrick scale is based on six (6) categories of skin as described below:

Type I	Light, pale white	Always burns, never tans
Type II	White, fair	Usually burns, tans with difficulty
Type III	Medium, white to olive	Sometimes mild burn, gradually tans to olive
Type IV	Olive, moderate brown	Rarely burns, tans with ease to moderate brown
Type V	Brown, dark brown	Very rarely burns, tans very easy
Type VI	Black, very dark brown to black	Never burns, tans very easily, deeply pigmented

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 and after treatment, Day 1, and during study visits on Days 7, 28, and 56.

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 Day 7 and Day 84 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 Days 56 and 84 to verify no significant changes in weight throughout the assessment of SMF changes during the study.

4.7 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 Day 1, 7, 28 and Day 84 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.

4.7.1 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]).

4.7.2 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).

4.7.3 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 84 days), if pregnancy is suspected.

4.8 Submental Fat Thickness using Calipers

The aim of caliper measurement is to evaluate fat reduction before and after treatment. At screening, caliper measurement will be made with the subject's head maintained in a neutral position. The caliper will be positioned to pinch the skin at 15 mm on either side of the center point of the submental area.

Additional measurement to assess efficacy will be conducted at study visits at Days 28, 56, and 84.

4.9 2-D Standardized Photography

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

Additional photography will be conducted on Days 1, 7, 28, 56, and 84 to evaluate qualitative changes in SMF area at study visits.

Photographs will be taken with a digital camera according to photography standards in dermatology surgeries for the face/neck area (see Appendix B).

4.10 Magnetic Resonance Imaging (MRI)

The purpose of the MRI exam is to evaluate fat reduction following treatment. MRI exams will be conducted in imaging centers close to selected clinical sites.

MRI will be conducted at screening in order to establish a baseline value for assessment of treatment efficacy. Post-treatment period MRI will be completed within 84 days (± 14 days) after the treatment session.

Quantitative measurements such as fat volume of the SMF area will be used as an objective parameter for measurement of SMF reduction following treatment.

Sagittal 2D and 3D images of the head and neck (chin area) will be obtained using 1.5 Tesla machine (General Electric, Siemens, Phillips or other). For each MRI visit, the total imaging time is expected to be approximately thirty (30) minutes.

During the imaging, subjects will be positioned in Head first Supine recumbent. Images in the sagittal plane across the entire submental region will be collected using an appropriate MR sequence to minimize the effects of air cavities, dental implants, and amalgam on the resultant MR image. This imaging approach will generate a 2D and 3D image data set that allows for the quantification of the SMF volume in several slices covering the treatment area. In the follow up MRI exam, slices will be positioned as similar as possible to the first MRI exam.

Images should be saved in a DICOM format and include the date completed and subject's screening number to be transferred home the Sponsor's request for central analysis.

Submental volume analysis will be performed by computer-assisted tools and calculation of submental volume will be completed prior to dosing and after treatment.

4.11 Clinician-Chin Assessment Tool (C-CAT)

SMF ratings using the C-CAT will be conducted by the Investigator at screening and baseline and at study visits on Days 28, 56, and 84 to assess the change in SMF severity before and following treatment.

The C-CAT score will be based on the Investigator's clinical evaluation of the subject in the Frankfurt horizontal plane. Clinical evaluation will include palpation of the chin and neck area, anterior, oblique and profile views of the chin and neck, and observation of pronation, supination, and lateral movement of the head. The score will be determined using the rating scale definitions. The score will be recorded as a whole number. At screening, the score will be used in conjunction with inclusion criteria.

The C-CAT is defined below. The scale is A 5-point scale (scored 0-4).

The grading system categorizes 3 aspects of submental chin fat: bulge, (size of the submental fat bulge) neck (extension of the bulge into the neck, downward and lateral) and jawline (the appearance of the jawline, presence of fat and definition of the jawline).

Each grade contains a description and a line drawing. Each grade is distinct and non-overlapping.

Clinician Chin Assessment Tool (C-CAT)

Score	Line Drawing	Description
0		• No bulge under chin • No fat in the neck • No fat along the jawline; jawline is visible and well defined
1		• Barely visible bulge, only visible in lateral and oblique views, not visible in frontal view • No fat in the neck • No fat along the jawline; jawline is visible and well defined
2		• Small but visible bulge, visible from all angles (lateral, oblique and frontal) • No fat in the neck • Fat may be present in the jawline; jawline is still visible and defined
3		• Noticeable bulge; visible in all angles (lateral, oblique and frontal) • Fat extends downward into the neck but does not extend to the laryngeal prominence (mid-neck) • Fat may extend laterally along the jawline; jawline is visible but may be poorly defined
4		• Very noticeable bulge, visible in all angles (lateral, oblique and frontal) • Fat extends down the neck to the laryngeal prominence and may extend beyond • Fat extends laterally along the jawline; jawline is poorly defined and may be indistinguishable from the neck

A comprehensive training guide with representative photographic examples and line drawing to each grade will be provided to the study center sites for training and visual comparison. The clinician training materials are attached in Appendix C.

4.12 Subject – Self-Chin Assessment Tool (S-CAT)

SMF ratings using the S-CAT will be conducted by the subject at screening and baseline and at study visits on Days 28, 56, and 84 to assess the change in SMF area following treatment.

The scale has 5 grades from 0 to 4. Each grade utilizing line-drawings and descriptors to identify 5 unique and non-overlapping grades.

The chin fat is categorized by the following features: bulge (size of the fat bulge) neck (extension of the bulge downward and laterally into the neck) and jawline (presence of fat and definition of the jawline).

Self Chin Assessment Tool (S-CAT)

Score	Line Drawing	Description
0		• No bulge under chin • No fat in the neck • No fat along the jawline; jawline is visible and well defined
1		• Barely visible bulge, only visible from the side, not visible in the straight ahead view • No fat in the neck • No fat along the jawline; jawline is visible and well defined
2		• Small but visible bulge, visible from the front and sides views • No fat in the neck • Fat may be present in the jawline; jawline is still visible and defined
3		• Noticeable bulge; visible from the front and side views • Fat extends downward into the neck but does not extend to the Adam's Apple (mid neck) • Fat may extend laterally along the jawline; jawline is visible but may be poorly defined
4		• Very noticeable bulge, visible from the front and side views • Fat extends down the neck to the Adam's apple (mid-neck) and may extend beyond • Fat extends laterally along the jawline; jawline is poorly defined and may be indistinguishable from the neck

Self evaluations should be made sitting in an upright position with the chin at a right angle (as illustrated in the line drawings). Mirrors will be used to see the chin, neck and jawline from both front and side views.

A comprehensive training guide with representative photographic examples and line drawing to each grade will be provided to the subjects.

The subject self -assessment training material are attached in Appendix D.

4.13 Subject's Satisfaction Questionnaire for SMF Appearance

SMF satisfaction questionnaire will be conducted by the subjects at in screening visit and study visits on Days 28, 56, and 84 to assess the subject's satisfaction with their SMF after treatment. Subjects will be asked the following questions and will score their satisfaction based on the grades below:

How satisfied are you currently with the appearance of your chin, neck and jawline area?

Score	**Grade**
0	Extremely Satisfied
1	Satisfied
2	Somewhat satisfied
3	Neither Satisfied nor Dissatisfied
4	Somewhat Dissatisfied
5	Dissatisfied
6	Extremely Dissatisfied

How happy are you with the appearance of your neck as it relates to your chin fat?

Score	**Grade**
0	Extremely Satisfied
1	Satisfied
2	Somewhat satisfied

3	Neither Satisfied nor Dissatisfied
4	Somewhat Dissatisfied
5	Dissatisfied
6	Extremely Dissatisfied

How satisfied are you with the result of your treatment*?

Score	**Grade**
0	Very dissatisfied
1	Dissatisfied
2	Somewhat dissatisfied
3	Somewhat satisfied
4	Satisfied
5	Very satisfied

How likely would you be to recommend this procedure to friends and family*?

Score	**Grade**
0	Not at all likely
1	A little likely
2	Somewhat likely
3	Very likely
4	Extremely likely

*subjects will be asked this question only at study visits on Days 28, 56, and 84

4.14 Subject's Impact Questionnaires

A set of questions will be asked to assess subject's impact based on their SMF appearance. This will be conducted by at screening and at study visits on Days 28, 56, and 84 to assess the change in SMF area following treatment.

A. How self-conscious are you about your appearance as it relates to your chin fat?

0-Not at all self-conscious
1-A little self-conscious
2-Moderately self-conscious
3-Very self-conscious
4-Extremely self-conscious

B. How bothered are you by the appearance of your chin fat?

0-Not at all bothered
1-A little bothered
2-Moderately bothered
3-Very bothered
4-Extremely bothered

C. How much do you think that the appearance of your chin fat effects your career or work life?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

D. How much does the appearance of your chin fat effect your relationships?

0-Not at all
1-A little bit
2-A Moderate amount
3-A great deal
4-An extreme amount

E. How much does the appearance of your chin fat effect your self-confidence?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

F. Do you feel self-conscious about the appearance of your chin fat when you look at photographs?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

G. Do you try to hide or camouflage your chin fat? For example, make-up and hair styles, beard hair, clothing or neck/head position?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

H. Do you feel self-conscious when you look at your chin fat in the mirror?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

I. How do you think the appearance of your neck effects your relationships?

0-Not at all
1-A little bit
2- A moderate amount
3-A great deal
4-An extreme amount

J. How heavy or thin do you think your chin fat makes you look?

0 - I look more than 10 pounds thinner than I am
1 - I look 10 pounds thinner
2 - I look 5 pounds thinner
3 - I look my weight
4 - I look 5 pounds heavier
5 - I look 10 pounds heavier
6 - I look more than 10 pounds heavier

4.15 Physician Global Assessment Improvement Scale (GAIS) and physician assessment

Investigators will assess the improvement in SMF following treatment by comparing the photographs of the subject taken at screening versus the photographs taken at study visits on Days 28, 56, and 84.

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

Global Aesthetic Improvement Scale (GAIS)		
Grade	**Degree**	**Description**
1	Very much improved	Optimal cosmetic result
2	Very improved	Marked improvement in appearance from the initial condition, but not completely optimal
3	Improved	Obvious improvement in appearance from the initial condition
4	No change	The appearance is essentially the same as the original condition
5	Worsened	The appearance is worse than the original condition

Clinicians will be asked which word best describes the amount of submental fat the subject has*:

- No fat
- Barely visible pocket of fat
- Small but visible pocket of fat
- Visible pocket of fat amount
- Large pocket of fat

*The question will be asked at screening and on study visits 28, 56 and 84 Days.

4.16 Subject Global Assessment of Change and subject self-assessment

Subjects will be asked to self-assess their SMF appearance and change.

At each study visit, the subject will be asked to assess their improvement degree based on the following questions:

A. Looking in a mirror today, how would you rate the amount of your submental (under the chin) fat from 1 (not fat) to 10 (extreme fat) using the numerical rating scale? *

1 2 3 4 5 6 7 8 9 10

No fat extreme fat

B. Subjects Global Self-Assessment of under the chin fat: Which word best describes the amount of your submental (under the chin) fat? *

- o No fat
- o Barely visible pocket of fat
- o Small but visible pocket of fat
- o Visible pocket of fat amount
- o Large pocket of fat

* questions will be asked at screening visit and on Days 28,56 and 84

At each study visit (Day 28,56 and 84), the subject will be asked to assess their improvement degree based on the following scale:

Score	Grade
0	Extremely improved
1	Very much improved
2	Improved
3	No Change
4	Worse
5	Very much worsened
6	Extremely worsened

4.17 Evaluation of Response

Evaluation of response will be conducted on Days 28, 56, and 84 following injection of RZL-012 or placebo.

4.18 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 evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures..

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 Day 84 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, Day 1, and during study visits on Days 7, 28, and 56.

6.0 PHARMACOKINETICS

No PK measures will be assessed during this study.

7.0 EFFICACY

Efficacy measures include the following:

- Efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using the C-CAT.
- Assessment of the reduction in SMF on Day 84 as compared to baseline using the caliper measured submental thickness, MRI measured SMF volume, and the S-CAT.
- Assessment of SMF improvement using the Physician global SMF assessment, GAIS, Subject Global Assessment of Change Scale, Subject Global Self-Assessment and subject satisfaction questionnaire, subject's impact 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 at pre-screening visit:

- C-CAT
- S-CAT
- 2D photography

The following study evaluations and procedures are required to determine eligibility in the second part of the screening visit:

- 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)
- Caliper measurement of SMF thickness
- MRI
- Physicians Global Assessment Question
- Subject's satisfaction questionnaire (appearance of submental area)
- Subject Global Assessment questions
- Subject's impact questionnaire

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)
- S-CAT
- C-CAT

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

8.3 Study Randomization

Subjects will be randomized to each treatment group according to a predefined randomization scheme in a ratio of 1:1:1 among eight (8) to twelve (12) clinical sites. 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
- AE assessment

8.5 Drug Administration

RZL-012 or placebo will be supplied as a single treatment in multiple sites of injection (32±4 injections). The injection dosing regimen and technique is crucial for the therapy safety.

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

1. The lower face and anterior neck 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. The treatment area will be bounded superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone.

4. 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.

5. An area of 32±4 adjacent injection points will be determined following the Investigator's evaluation.

6. Syringes will be filled with 1 mL RZL-012 high dose or low dose or placebo and the number of syringes will be compatible with the total volume of injection. Up to six (6) syringes for a total volume of 5.4 mL will be used.

7. All injections will be administered perpendicularly in 90 degrees, using a 1 mL Luer-lock syringe and a 29G x 1/2" needle, respectively.

8. 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.

9. 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.

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

The injection pattern used will be based on an existing grid in the shape of the submental area, where distance between injection rows will be 1 cm and distance between the injection columns will be 1 cm.

The number of injections for each subject will be determined by the Investigator according to fullness of SMF but will not be lower than 28 injections or higher than 36 injections.

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

- RZL-012 low dose will be provided in vials of 163 mg/4.8 mL (34 mg/mL)
- RZL-012 high dose 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)

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 seated in the injection position for an additional ten (10) minutes after injections. Subjects will remain in the clinic up to 30 minutes (15-30 minutes) post dosing for medical supervision and AE assessments. During the confinement period, there are no restrictions in terms of activity or diet.

8.7 Study Visits (Days 1, 7, 28, and 56)

Subjects will return to the clinical site for study visits on Days 1, 7, 28, and 56. Study visit assessments include the following:

- Vital signs
- Concomitant medication
- AEs
- Weight measurement (Day 56)
- Clinical laboratory tests (Days 1, 7, 28)
- Serum pregnancy test (in case pregnancy is suspected)

- ECG (Day 7)
- Caliper measurement of submental thickness (Days 28 and 56)
- S-CAT (Days 28 and 56)
- C-CAT (Days 28 and 56)
- 2D Photography (Days 1, 7, 28, and 56)
- Subject Global Assessment of Change (Days 28 and 56)
- Subject's satisfaction questionnaire (Day 28 and 56)
- Physician GAIS (Days 28 and 56)
- Subject impact questionnaire (Day 28 and 56)

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 (Day 84)

Final study visit assessments include the following:

- ECG
- Physical Exam
- Concomitant medication
- AEs
- Clinical laboratory tests (including serum pregnancy test, in case pregnancy is suspected)
- Weight measurement
- Caliper measurement of submental thickness
- S-CAT
- C-CAT
- MRI
- 2D Photography
- Physician GAIS and physician assessment
- Subject Global Assessment of Change and self-assessment
- Subject's satisfaction questionnaires
- Subject impact questionnaires

8.9 Additional follow up of subjects:

Following the completion of Day 84 visit of the last subject, subjects from three (3) chosen clinical sites will be followed up further twice up to a 1 year after injection to assess long term safety and duration of efficacy. The additional follow up visits will be at 6 and 12 months after injection.

These visits will include the following procedures:

- 2D Photography
- Physical exam of the treated area
- S-CAT
- C-CAT
- 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, illustrated in Figure 1, 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) and 163mg/4.8 mL (34 mg/ml).

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

RZL-012 will be provided in 2 strengths of 240 mg/4.8 mL (50 mg/mL) and 163 mg/4.8 mL (34 mg/mL).

The placebo is a ready to use liquid to be injected into the subcutaneous fat, supplied in a 1 vial 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 29 G ½" sterile needle for a maximal low dose of 183.6 mg and a maximal high dose of 270 mg. 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) and 163mg/4.8 mL (34 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. Used sprayers will be accounted for and disposed appropriately.

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 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 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 edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures..

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 (Table 5).

The reporting period for AEs starts after dosing of study drug and will end at final study visit on Day 84. At study completion, after the Day 84 visit of the last subject, subjects at 3 chosen clinical sites will be followed up at 6 and 12 months after injection to follow safety and duration of efficacy.

If an AE remains unresolved at discharge, subject will be scheduled for a visit that will be held 6-8 weeks after study termination to verify the resolution of AE. On that visit, follow up of efficacy using C-CAT and S-CAT will also be conducted. In case the AE will not resolved following that visit, 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 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	**Robert Hasson**
Mobile: 1-805-705-5853	Mobile: 1-619-540-6253

Email: dr.patricia.walker@gmail.com	Office: 1-858-368-9925
	Fax: 1-858-436-1401
	Email: rhasson@pacificlinkconsulting.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.

11.2.4 Internal Safety Committee

An internal safety review committee will review the safety data collected during the study in a blinded manner. The committee members will include study medical monitor, Raziel's CMO and clinical director.

The meeting will be held when every enrolled 40 subjects completed Day 7. Summary of the safety including all subjects up to that point may be reviewed as well. Following completion of enrollment of all subjects, the committee will meet quarterly during the follow up period.

The study enrollment will be suspended if either of the following occur:

- Greater than 20% of subjects report a drug related grade 3 (severe) adverse event for a period duration of more than 28 days after injection. Of note severe swelling is may be during the first 24 – 96 hours after injection.
- >1 subject with a drug related CTCAE Grade of 4 or 5

In the event of the above, the enrollment and treatment will be suspended, the safety committee will review all data to examine potential safety issue. Additional experts may be brought in to review safety data if deemed necessary by the safety committee. A safety report will be issued with the conclusions of the meeting. The recommendation of the safety committee will be documented. Potential outcomes are reinitiating enrollment with current safety practices, reinitiating study with caveats (e.g. additional precautions/limitations or safety training), stop enrollment.. For each internal safety committee meeting, report will be prepared by the medical monitor that include data about enrollment, list of SAEs, summary of AEs.

12.0 STATISTICAL CONSIDERATIONS

12.1 Sample Size Determination

A total of 135 subjects will be included in the study, divided into three (3) groups: RZL-012 low dose (up to 183.6 mg/5.4 mL), RZL-012 high dose (up to 270 mg/5.4 mL) and placebo (up to 5.4 mL) with 45 subjects in each group.

For the primary endpoint (proportion of high dose group subjects who have at least a 1-grade improvement from baseline to Day 84 on the C-CAT scale), the assumed true rates are 70% in the RZL-012 high dose group and 35% in the placebo group (a difference of 35 percentage points). Based on the use of a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance, 41 subjects per group are required at 90% power. In order to account for a dropout rate of up to ~9%, the planned sample size is 45 subjects per group, for a total sample size of 135 subjects.

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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).

For the primary endpoint analysis, Pearson's chi-square test will test the statistical significance of the difference in the proportion of responding subjects between the high dose RZL-012 group and the placebo group. A responder is defined as a subject who has at least a 1-grade improvement between Day 84 and baseline on the C-CAT.

Secondary endpoints (improvement in 1 point in S-CAT and C-CAT, improvement in 2 points in both S-CAT and C-CAT) will be tested using a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance. If the primary analysis is not statistically significant, then the results of the secondary analysis will be exploratory rather than confirmatory.

All other secondary endpoints will be tested using a two-sided test at the alpha=0.05 level of significance.

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, weight, blood parameters, ECG (QT).

AE assessment and treatment area evaluation including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, 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 (Table 5).

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

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.

15.0 REFERENCE LIST

1. Jones DH, Carruthers J, Joseph JH, et al. REFINE-1, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial with ATX-101, an injectable drug for submental fat reduction. Dermatol Surg. 2016;42:38–49.
2. Duncan D, Rotunda AM. Injectable therapies for localized fat loss: state of the art, clinics in plastic surgery. Clin Plast Surg. 2011;38:489–501.
3. Humphrey et al, ATX-101 for reduction of submental fat:A phase III randomized controlled trial, J AM ACAD DERMATOL Volume 75, Number 4 (2016), PP 788-797.
4. Dover et al, Management of Patient Experience With ATX-101 (Deoxycholic Acid Injection) for Reduction of Submental Fat, American Society for Dermatologic Surgery,42:11S:NOVEMBER SUPPLEMENT 2016
5. Kaneti L, Bronshtein T, Malkah Dayan N, Kovregina I, et al. Nanoghosts as a Novel Natural Nonviral Gene Delivery Platform Safely Targeting Multiple Cancers. Nano Lett 2016 Mar 9;16(3):1574-82.
6. Oieni J, Levy L, Letko Khait N, Yosef L, et al. Nano-Ghosts: Biomimetic MembranalVesicles, Technology and Characterization. Methods. 2020 May 1;177:126-134.

Appendix A: Schedule of Study Procedures

Table 1: Schedule of Study Procedures

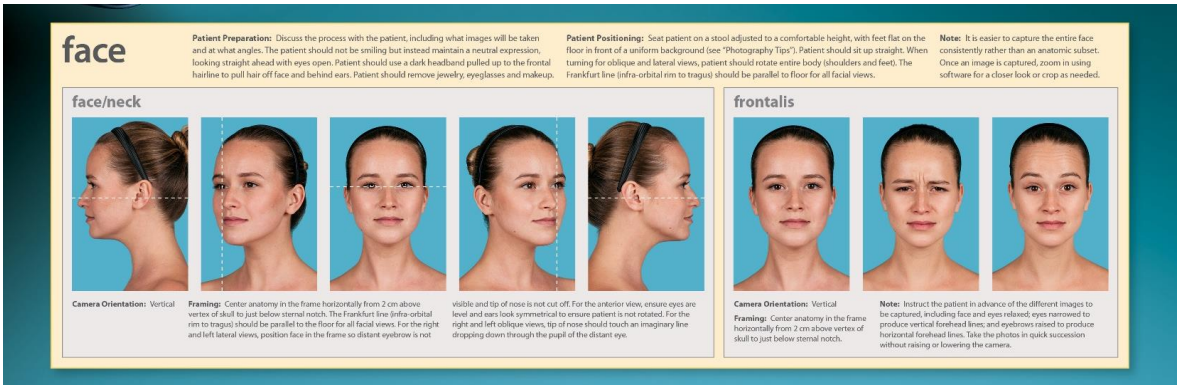
Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Additional follow up of RZL-012 treated subjects (6 and 12 months after injection)**	
Study Day[a]	**Day (-28) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**6 months**	**12 months**
Signed informed consent	X								
Medical history	X								
Physical Exam[b]	X						X	X[h]	X[h]
Concomitant Medication	X	X	X	X	X	X	X		
Pregnancy ß-hCG	X								
Pregnancy urine test (women)[c]		X							
Caliper measurement of submental fat	X				X	X	X		
Weight measurements	X	X				X	X		
Hematology and Chemistry[d]	X		X	X	X		X		
ECG	X			X			X		
Vital signs	X	Pre[e] X post[e]	X	X	X	X			
Injection of RZL-012		X							

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Additional follow up of RZL-012 treated subjects (6 and 12 months after injection)**	
Study Day[a]	**Day (-28) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**6 months**	**12 months**
Clinician Chin Assessment Tool (C-CAT)	X	X			X	X	X	X	X
Subject- Self-Chin Assessment Tool (S-CAT)	X	X			X	X	X	X	X
Physician Global Assessment Improvement Scale (GAIS) and physician global assessment	X				X	X	X		
Subject's Satisfaction questionnaire for SMF appearance	X[g]				X	X	X		
Subject's impact questionnaire	X				X	X	X		
Subject Global Assessment of Change and subject self assessment	X				X	X	X		

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Additional follow up of RZL-012 treated subjects (6 and 12 months after injection)**	
Study Day[a]	**Day (-28) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**6 months**	**12 months**
2D Standardized photography	X		X	X	X	X	X	X	X
MRI	X[f]						X		
AEs		X	X	X	X	X	X	X	X

a. Study day is based on Day 0 defined as the day of RZL-012 injection.
b. Including Fitzpatrick skin type, height, BMI
c. 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
d. In case of clinically significant values at any visit, an unscheduled visit will be added
e. Pre/post – refers to before/after injection, respectively
f. MRI (performed during screening period) will be conducted after subject qualifies on all screening criteria. Post-treatment period MRI will be completed 84 days (± 14 days) after the subject's last treatment session.
g. Subjects will be asked on their neck appearance satisfaction at screening visit
h. Physical exam will be done only to the treated area

Appendix B: Photographic Standards of the Face Area



Appendix C: Clinician Chin Assessment Tool

RZL-SFSD-US-001_C-CAT.pdf

Appendix D: Subject Chin Assessment Tool

RZL-SFSD-US-001_S-CAT.pdf