RZL-012 Study Protocol

Protocol Number RZL-012-SMF-P2aUS-001

A Single Blind, Randomized, Placebo-controlled, Phase 2, 2-cohort Study for the Evaluation of Efficacy and Safety of RZL-012 for Submental Fat Reduction in Healthy Volunteers

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Confidentiality Statement

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body Mass Index
BUN	Blood urea nitrogen
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EF	Efficacy analysis set
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IND	Investigational New Drug
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
NOAEL	No observed adverse effect level
PI	Principal Investigator
PK	Pharmacokinetics
QOL	Quality of life
SA	Safety analysis set
SAE	Serious adverse event
SFM	Subcutaneous fat mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
US/USA	United States/United States of America

STATEMENT OF COMPLIANCE

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

INVESTIGATOR SIGNATURE PAGE

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

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

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

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

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

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

_____	_____	_____
Investigator's name	Investigator’s Signature	Date

PROTOCOL SYNOPSIS

Protocol Number	RZL-012-SMF-P2aUS-001
Protocol Title	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.
Study Phase	Phase 2a
Study Drug	RZL-012
Study Objectives	Primary objective: To evaluate the safety of RZL-012 subcutaneous injections in the submental area, relative to placebo, as assessed by spontaneous adverse event reports and post injection evaluation of subjects by treating physician. Secondary objectives: To evaluate the efficacy of RZL-012 subcutaneous injections in the submental area, relative to placebo, by: 1. Evaluation of treatment efficacy by using Physician's global assessment questionnaire, on study days 28, 56 and 84 2. Reduction from baseline in submental fat volume, as measured by MRI 3. Improvement in subject's satisfaction rating score of the FACE-Q questionnaire on study days 28, 56 and 84 vs. baseline
Sample Size	Twenty-Eight (28) subjects (12 for cohort 1 and 16 for cohort 2) will be included in the study. Subjects in each cohort will be injected with a different dose. The total of 28 subjects will be enrolled in 2 clinical sites.
Study Design	This is a single blinded, randomized, placebo-controlled, 2-cohort clinical study in healthy volunteers. Cohort 1 will be comprised of 8 active (RZL-012) and 4 placebo subjects. Cohort 2 will be comprised of 16 subjects that will be randomized for active treatment and placebo. All subjects will receive a single dose of RZL-012 or vehicle into the submental area, after which they will be monitored for safety and efficacy during 84 days of follow-up. All subjects per cohort will be randomized to either active treatment or placebo at a ratio of 2:1 per cohort. Subjects will be blinded to study treatment while physicians will not be blinded. The study will be composed of 2 treatment cohorts, 12 in cohort 1 and 16 in cohort 2. The study will be conducted in 2 clinical sites. In cohort 1, a total of 12 subjects and in cohort 2 a total of 16 subjects will be randomized to receive active or placebo treatment (2:1) according to a randomization program that will be prepared prior to study initiation. Each clinical site will have at least one active and one placebo treatment subject per each study cohorts. In case of slow enrollment in one of the sites, other sites may complete the enrollment of subjects in each cohort. Cohort 1 (N=12) – Each subject will be dosed with up to 120 mg RZL-012 (depending on submental fat area) or vehicle. Cohort 2 (N=16) – Each subject will be dosed with up to 240 mg RZL-012 (depending on submental fat area) or vehicle. Treatment of cohort 2 will start following cohort 1 day 28 data. An independent Data Safety Monitoring Board (DSMB) will review safety and tolerability data for cohort 1 subjects, 28 days after injection, and decide whether it is safe to increase the dose for the next study cohort. The decision to proceed to the cohort 2 will be made within 30 days (28 days + 2 days) after injection of the last dosed subject in cohort 1. The DSMB will be comprised of two independent MDs with expertise in the aesthetic area

	and in conduction of clinical trials. In case of serious safety concerns (e.g., prolonged severe swelling or severe pain following injection) among cohort 1 subjects receiving the 120 mg dose, sponsor and DSMB may decide to reduce or stay with the 120 mg/subject dose level for cohort 2 subjects.
Study Population	Men and women 18-65 years old
Main Inclusion Criteria	Subjects must meet all the following to be eligible for study participation: 1. Men and women 18-65 years old. 2. Subjects with Body Mass Index <35. 3. Subjects must have submental skin fold thickness greater than 1.5 cm as measured with calipers. 4. Males must be willing to be clean shaved for all study visits. 5. Patient weight must be stable (no fluctuation of >15 pounds in the past year). 6. Males or females in the age of fertility agree to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012. 7. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study. 8. Subjects must sign an IRB approved informed consent indicating they are aware of the investigational nature of the study.
Main Exclusion Criteria	Subjects meeting any of the following criteria will be excluded from study participation: 1. Unable to tolerate subcutaneous injection. 2. Pregnant or lactating women. 3. Subjects with dysfunctional gallbladder activity, e.g., underwent cholecystectomy or cholecystitis. 4. Any uncontrolled systemic disease -a potential patient in whom therapy for a systemic disease is not yet stabilized will not be considered for entry into the study. 5. Treatment with botulinum toxin injections in the neck or chin area within 6 months before screening. 6. Excessive submental skin laxity. 7. Any Scars, unshaven hair, tattoos or jewelry on or near the proposed treatment area. 8. Significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would preclude enrollment into the study. 9. An active dermatitis or open wound in the proposed treatment area. 10. An active bacterial, fungal, or viral infection in the proposed treatment area. 11. Pre-existing skin condition in the submental region that may confound evaluation or analysis, at investigator discretion. 12. Previously treated with focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate to the submental region within the previous 6 months. 13. Pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia or facial nerve palsy. 14. Pre-existing medical condition other than increased submental fat that may result in increased submental fullness such as but not limited to thyroid enlargement, goiter, cervical lymphadenopathy etc., at investigator discretion. 15. Must not have a planned fat reduction procedure of any variety to the submental region for the duration of the study. 16. Must not have planned significant alterations in diet or physical activity that may result in significant fluctuations in weight. 17. Subjects with medication or history of coagulopathy. 18. Allergic subjects to Benadryl.

19. Subjects treated chronically at least 3 months prior to study entry with systemic steroids or immunosuppressive drugs.
20. Subjects treated chronically at least one week prior to study entry with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
21. Current participation or participation within 3 months prior to the start of this study in a drug or other investigational research study.
22. Claustrophobia or MRI incompatible device or implant.

Study Drug Dosage and Administration

All subjects will receive a single multi injection of the investigational product RZL-012 or placebo in accordance with the table below:

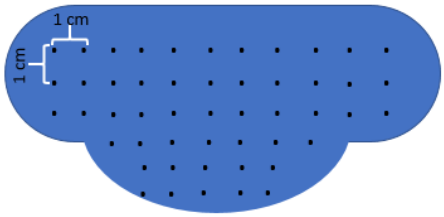
	N=28	
	Cohort 1 N=12	Cohort 2 N=16
Number of RZL-012/Placebo	8/4	At least 4 placebo subjects
Total Maximal Dose RZL-012 (mg)/vehicle (mL)	Up to 120 mg/2.4 mL	Up to 240 mg/4.8 mL
Dose of RZL-012 (mg)/vehicle (mL) per single injection	2.5 mg/0.05 mL	5 mg/0.1 mL
Maximal Number of Injections per subject	48	48

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.

Cohort 1 active subjects will receive a maximal dose of up to 120 mg RZL-012 in a series of up to 48 injections. Each injection point will be dosed with 2.5mg RZL-012 (0.05ml of RZL-012 solution). Placebo (vehicle) subjects will be injected with 0.05 mL vehicle at each injection site, resulting in a total volume of up to 2.4 mL.

Cohort 2 active subjects will receive a maximal dose of up to 240 mg RZL-012 in a series of up to 48 injections. Each injection point will be dosed with 5 mg RZL-012 (0.1 mL of RZL-012 solution). Placebo (vehicle) subjects will be injected with 0.1 mL vehicle at each injection site, resulting in a total volume of up to 4.8 mL.

The injection pattern in cohort 1 and cohort 2 will be based on a submental area shaped grid in which the distance between rows will be 1cm and distance between columns will also be 1 cm as seen in the figure below. Physician will choose two points at the edge of the 50-point pattern that will not be injected (up to 48 injections):



Injection pattern to be used by the physician for precise dosing into submental fat area in both study cohorts. The dose at each injection site will be different between Cohort 1 and Cohort 2, i.e., 0.05 mL injection volume in cohort 1 and 0.1 mL injection volume in Cohort 2 for active treatment or vehicle.

Twelve (12) subjects from cohort 1 (8 active and 4 placebo) will be injected with a maximal dose of 120 mg/subject or with up to 2.4 mL of vehicle. If no serious safety concerns will be noted within 28 days of follow-up post-dose of subjects from cohort 1, the study will proceed

	to the additional 16 subjects of Cohort 2. These subjects will be injected with a maximal dose of 240 mg/subject or with up to 4.8 mL of vehicle. In case of serious safety concerns (e.g., prolonged severe swelling or severe pain following injection) among Cohort 1 subjects receiving the 120 mg dose, sponsor and DSMB may decide to reduce or stay with the 120 mg/subject dose level for Cohort 2 subjects. Subjects will be injected with RZL-012 or vehicle perpendicularly (90°) to the skin. An ice pack will be placed on the injected area for pain relief immediately after injection. Subjects will have to remain seated in the injection position for an additional 10 minutes after dosing.
Study Procedure	Activities upon study entry will include: Informed consent, medical history, physical examination, measurement of submental skin fold thickness with calipers, weight measurements, vital signs, MRI. Subjects will be randomized upon eligibility to RZL-012 or placebo at each clinical site and each cohort according to a predefined randomization scheme. Periodic site visits will allow assessment of treatment safety (skin adverse events) and efficacy. Subjects will be advised to continue their regular diet and physical activity.
Visit Schedule	Subject site visits will be performed ± 1 days from scheduled dates (from Day 7 visit to Day 84 visit). **Screening visit (Day -45 through -1):** - Following signing the informed consent - assessment of subject eligibility will include: medical history, physical examination, weight measurements, height measurement, BMI record, pregnancy elimination by women subjects, vital signs, measurement of submental fat thickness using calipers, skin type by Fitzpatrick scale and MRI. MRI will be conducted within a window of 5 days from the screening visit but prior to baseline visit. **Baseline visit (Day 0):** - Pre-treatment: eligibility confirmation, concomitant medications, vital signs, weight measurement, Pregnancy test, Draize score of the injection site area, pain, bruising and induration grading, FACE Q questionnaire, 2D Photography. - Treatment - All injections will be administered 90° to the skin surface using a 0.5 mL (cohort 1) syringe or 1 mL (cohort 2) Luer-lock syringe and a 29/30 G x 1/2" needle, respectively (the hole of the needle pointing into the fat layer). The injection pattern will be performed according to physician evaluation of submental fat fullness. At the end of treatment, subjects will remain seated for an additional 10 minutes in the same position. - Post treatment: Draize score (2h post injection ± 30 min), adverse events (AEs) record (including pain, bruising and induration grading) . **Schedule visits (Day 1-84):** - At Day 1 following treatment: Concomitant medications, vital signs, Draize score, AEs (including pain, bruising and induration grading). - At Days 7 and 14 following treatment: Concomitant medications, vital signs, Draize score, 2D photography of face, AEs (including pain, bruising and induration grading). - At Day 28 following treatment: Concomitant medications, vital signs, Draize score, 2D photography of face, Subject's satisfaction questionnaire (Face Q), Physician's global assessment questionnaire, AEs (including pain, bruising and induration grading). - At Day 56 following treatment: Concomitant medications, vital signs, weight, Draize score, 2D photography of face, Subject's satisfaction questionnaire (Face Q), Physician's global assessment questionnaire, AEs (including pain, bruising and induration grading). - Day 84 visit: Concomitant medications, Weight, Draize score, 2D photography of

	face, Subject's satisfaction questionnaire (Face Q), Physician's global assessment questionnaire, MRI, AEs (including pain, bruising and induration grading). MRI at Day 84 visit will be performed at Day 84±5 Days.
Safety Analysis	Safety data from the study will be summarized descriptively by treatment and by cohort. The nature, frequency, seriousness, severity and relation to study drug of adverse events (AE) will be tabulated for all subjects combined and by treatment. Draize scores will be presented in tabular format by visit and cohort.
Study Endpoints	**Primary Endpoint**: The main objective is to evaluate safety following injection of RZL-012 vs. placebo into submental fat. Skin irritancy and AEs related to the injection procedure will be evaluated for frequency, severity and duration. Specifically, tolerability and assessment of the following AEs will be monitored: bruising, pain, induration erythema and swelling/edema at the injection site. **Secondary Endpoints**: Secondary endpoints will test the efficacy of RZL-012 vs. placebo according to the following measures: 1. Improvement of Physician's global assessment questionnaire for treatment efficacy in active vs. placebo treated subjects on Days 28, 56 and 84 following injection. 2. Reduction from baseline in submental fat volume, as measured with MRI, in RZL-012 treated subjects vs. placebo treated subjects on Day 84 following injection. 3. Improvement from baseline in the Face-Q satisfaction questionnaire rating score in RZL-012 treated subjects vs. placebo treated subjects on Days 28 and 56 and 84.
Statistical Methods	Study data will be tabulated and summarized using the mean, standard deviation or standard error. AEs related to injection and Draize scores will be presented in tabular format by visit, cohort and treatment (active vs. placebo). Improvement in Global physician's scale score pf RZL-012 treated subjects vs. placebo treated subjects by cohort and overall. The average change from baseline in submental volume as analyzed from MRI images will be presented in a tabular form by treatment received (RZL-012 / placebo), by cohort and overall. The average change from baseline in questionnaire score will be presented in a tabular form by treatment received (RZL-012 / placebo), by cohort and overall. Any statistical tests will be two-sided. The required significance level (P value) of findings will be equal to or lower than 5%.
Study Duration	Study duration is 4.5 months for each subject, including enrollment, treatment and follow-up period.
Study Sites	2

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

Submental fat represents an aesthetic problem in overweight males and females. Although localized fat deposits are present in many parts of the body, submental fat is particularly noticeable due to its location. Until recently, treatments of submental fat 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 injection was approved as a treatment for submental fat. However, due to repeated treatments (every 4 weeks, 4-6 treatments) and adverse events such as swelling and bruising that repeats after every treatment, physicians and subjects are still searching for additional alternatives in the market.

Raziel Therapeutics has discovered that a novel synthetic molecule (termed RZL-012) can help reduce fat content in human and pigs. Recent data has led Raziel to the understanding that the 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 probably due to a local inflammatory reaction. 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 showed a different pattern compared with liponecrosis and inflammation - 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.

Recently, RZL-012 was evaluated as a treatment for local fat reduction among obese and overweight subjects in two clinical studies and was evaluated for the treatment of fat disorders diseases such as Dercum's Disease (DD) and lipedema.

In the initial exploratory clinical trial that was conducted (RZL-012-P0US-001.3 under IND 119941) to test safety and thermogenesis-induction of RZL-012 in overweight and obese subjects, RZL-012 was found to be safe with mainly transient and local adverse events (AEs). A thermogenic effect (a rise of 1 °C in temperature at the injected site compared to the untreated collateral side) was evident in the RZL-012-treated subjects of the highest dose cohort

(20 mg/subject). Moreover, MRI at 28 days after injection demonstrated that fat mass was reduced at the injection site compared to matched fat mass at the non-injected contralateral site, in RZL-012 but not in vehicle-treated subjects.

In a Phase 2a study that was conducted in 32 overweight and obese subjects (RZL-012-P2aUS-001.4 under IND 133324), the maximum injection dose of RZL-012 was 180 mg/subject. RZL-012 demonstrated a dose dependent reduction in Subcutaneous Fat Mass (SFM) ratio at doses of 80 mg/subject (8.6% ± 3.6% reduction), 120 mg/subject (10.5% ± 3.4% reduction) and 180 mg/subject (18.1% ± 4.9% reduction) vs vehicle (3.6% ± 1.6% increase), 56 days following injection. The reduction of local fat mass was still evident 6 months following RZL-012 injection. Safety and tolerability were good with only mild or moderate adverse events, mostly transient and localized to the injection site.

An additional Phase 2a study (RZL-012-FD-P2aUS-001.7 under IND 135762) was conducted to evaluate the safety and pharmacodynamic response to RZL-012 in lipedema and DD patients. Interim analysis for 5 of 6 DD subjects demonstrated a 55% reduction in height of 18 injected lipomas. Safety and tolerability were good with mild or moderate adverse events. The Adverse Events (AEs) that were categorized as definitely related to the study drug were transient and localized to the injection site.

Based on the above, Raziel concludes that the safety profile of RZL-012 is good and acceptable and the compound demonstrated efficacy in long-term reduction of local SFM. Thus, Raziel Therapeutics is being developed to be for aesthetic indications such as submental fat.

1.1.2. RZL-012 Formulation Development

The active ingredient RZL-012 drug substance was manufactured by Pharmacore, High Point NC, USA. The drug product, 5 % RZL-012 in F12 liquid formulation (RZL-012 in F12 formulation is 250 mg RZL/5 mL vial = 50 mg RZL/mL) was manufactured and packed at Nextar Ltd, Ness-Ziona, Israel. RZL-012 in F12, which was once defined as RZL-012 F12, is now defined as RZL-012. The active ingredient and formulation manufacturing and packing were in accordance with current Good Manufacturing Practices (cGMPs).

1.2. NONCLINICAL ASSESSMENTS

1.2.1. Pharmacology

Studies pigs concluded that RZL-012 mechanism of action (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. Efficacy In-vivo Studies

Several nonclinical studies in pigs, in which the subcutaneous fat tissue 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 injection 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 at 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 h post dose. RZL-012 did not affect any of the parameters tested; hence it was concluded that RZL-012 has no effects on the respiratory system at the tested dose of 10 mg/rat.

A board-certified veterinary cardiologist conducted a qualitative and quantitative review of the electrocardiograms (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 haematological 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

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

1.2.4. Clinical Studies

RZL-012 has been tested in several clinical trials. A total of 54 subjects were exposed to RZL-012 at single doses of up to 180 mg. The currently planned clinical trial will be the first trial to test a single maximal dose of RZL-012 of up to 240 mg, (the NOAEL) and the first trial to assess the potential efficacy of RZL-012 in reducing submental fat.

Two studies were completed and one study is still on-going.

Table 1: 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
RZL-012-FD-P2aUS-001.7 **ON GOING**	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 will receive up to 40 mg RZL-012 Cohort 2 Lipedema: Each 3 subjects will receive 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

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 at the baseline visit till the following day (Day 0-1).

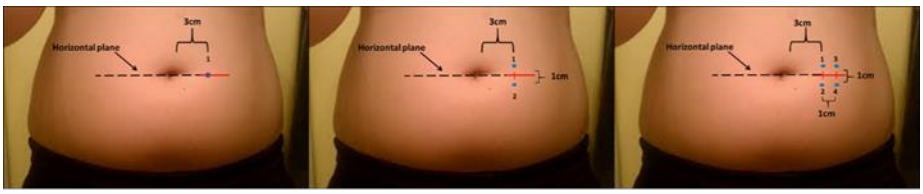
The primary objective of the study was the evaluation of the overall safety of RZL-012 after subcutaneous injection and the existence of a thermogenic effect. A thermogenic effect was defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the contra-lateral (non-injected 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 where in each cohort 8 subjects were injected (6 active and 2 control). This was a dose escalation study, therefore RZL-012 was injected at doses of 5, 10, and 20 mg/subject at cohorts 1, 2, 3, respectively.

Subjects received a single treatment in multiple sites (1-4) of injection diagonally (45°) to the skin surface at 3 cm lateral to the umbilicus lateral wall. The distance between injected sites was 1 cm (see Figure 1).

Figure 1: Injection Sites for Phase 0 Study



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

RZL-012-P0US-001.3 Study Results:

RZL-012 was generally found to be safe in all cohorts. There were no clinically significant changes in vital signs, ECG and almost all blood laboratory tests. Most AEs associated with RZL-012 injection were confined to the injection site and were transient. Biopsy from the injection site revealed no damage to the skin 56 days following RZL-012 injection. The only

significant local AE was an abscess in one subject in the lower abdomen at the surrounding of injected side (but away from the injected site).

One systemic clinically significant AE involved a severe elevation of 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.

Magnetic Resonance Imaging (MRI) results demonstrated a decrease over time in Subcutaneous Mass Fat (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:

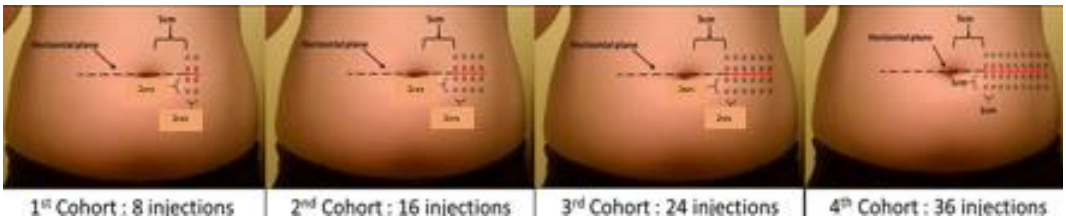
1. Duration of the thermogenic effect, defined as a net-delta ≥ 1.
2. Local reduction in fat mass as determined by MRI.

3. Clinical laboratory changes from baseline
4. Establishing the pharmacokinetic 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 1cm in Cohort 4 as seen in Figure 2.

Figure 2: Injection Sites for Phase 2A Study



RZL-012-P2aUS-001.4 Study Results:

In the current 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 seems 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 found due to the subcutaneous injection of RZL-012, was elevation in d-dimer values at the highest injected dose, 180 mg. However, this increase was transient, up to 3 days after injection, and non-clinically significant.

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 vs. Placebo. Among Cohort 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 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 concludes that the risk benefit profile of RZL-012 as seen in 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 such as excess in submental fat.

1.2.4.1.3. Protocol No. RZL-012-FD-P2aUS-001.7 Status: ongoing

An additional ongoing clinical trial is 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 is to evaluate the overall safety of RZL-012 following injection into the subcutaneous fat in patients with lipedema or DD.

The secondary objective is 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.

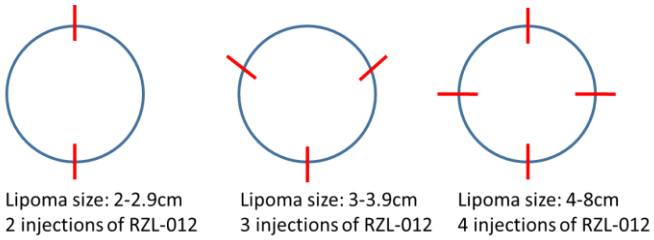
The study is composed of 2 cohorts where the 1st cohort is comprised of 6 subjects with Dercum's disease and the 2nd cohort is comprised of subjects with lipedema subjects having substantial fat above the knee.

1st Cohort Dercum's disease:

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

Subjects received a single treatment in multiple sites (2-8 cm lipoma size) of injection according to the design in Figure 3.

Figure 3: Injections Diagram According to Lipomas Size



2nd cohort 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 adding up to 12 injections of 60 mg RZL-012 (1/4th the NOAEL based on Human Equivalent Dose (HED) from GLP toxicology study).

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 adding up to 16 injections of 80 mg RZL-012 (1/3rd the NOAEL based on HED from GLP toxicology study), see Figure 4.

Figure 4: Injection Scheme Lipedema Subjects

RZL-012-FD-P2aUS-001.7 Interim Study results:

As of April 2019, all 12 subjects from both cohorts were recruited and injected with study drug.

Results for lipedema subjects are still pending.

Below are the interim results of 5 subjects with Dercum's disease. A total of 18 lipomas were injected with RZL-012 and followed up for 56 days for lipoma size changes and pain scores.

Among the 5 subjects who completed the study, there were no clinically significant changes in vital signs, ECG and blood laboratory parameters. A total of 11 AEs was reported; 54% of the AEs were categorized as mild and 46% were categorized as moderate. No severe AEs were reported. Injection site pain constituted 27% of the AEs and were categorized as moderate and considered as definitely related to the study drug. The remaining AEs were considered as unrelated or unlikely to be related to the investigated study drug.

Assessment of lipoma size change was performed using ultrasound measuring the height, width and length of each injected lipoma at Baseline, Day 28 and Day 56 visits. Lipoma dimension changes were best characterized by lipoma height. Out of 18 lipomas treated with RZL-012, 8 lipomas were completely eliminated at Day 56. All the eliminated lipomas were without fibrotic tissue in their capsule. The other lipomas demonstrated a height reduction of up to ~60%. An overall reduction of 55% in lipomas height was measured at Day 56 visit vs. baseline.

Based on the results described above it seems that RZL-012 is more effective in reducing lipomas that contain only fat tissue than those containing fibrotic tissue.

Pain assessment per individual lipomas was performed using a Comparative Pain Scale with numerical limits of 0-10 where 0 is rated as 'no pain' and 10 is rated as 'unimaginable pain'.

Pain associated lipomas had an overall reduction of 74.6% at Day 56 vs. screening. Four (4) out of 5 subjects demonstrated significant pain reduction (from averaged pain score of 4.6 at screening vs. average of pain score of 0.5 at Day 56, according to comparative pain scale). Only one subject (subject 1001) did not demonstrate any change in pain at Day 56.

Based on interim data, Raziel Therapeutics believes that RZL-012 can be beneficial for treating patients with fat disorders such Dercum's disease.

Further details of clinical trials results are described in the IB.

2. PURPOSE AND STUDY OBJECTIVES

2.1. PURPOSE

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.

2.2. STUDY OBJECTIVES

2.2.1. Primary

To evaluate the safety of RZL-012 subcutaneous injections in the submental area, relative to placebo, as assessed by spontaneous adverse event reports and post injection evaluation of subjects by treating physician.

2.2.2. Secondary

The secondary objectives are to evaluate the efficacy of RZL-012 subcutaneous injections in the submental area, relative to placebo by:

- Evaluation of treatment efficacy by using Physician's global assessment questionnaire, on study Days 28, 56, and 84
- Reduction from baseline in submental fat volume, as measured by MRI
- Improvement in subject's satisfaction rating score of the FACE-Q questionnaire on study Days 28, 56, and 84 vs. baseline

3. STUDY DESIGN

3.1. DESCRIPTION OF STUDY DESIGN

This is a single blinded, randomized, placebo-controlled, 2-cohort, clinical study in healthy volunteers.

Cohort 1 will be comprised of 8 active (RZL-012) and 4 placebo subjects. Cohort 2 will be comprised of 16 subjects. That will be randomized to receive active or placebo treatment All subjects will receive a single dose of RZL-012 or vehicle into the submental fat, after which they will be monitored for safety and efficacy assessments across 84 days of follow-up. All subjects per cohort will be randomized to either active treatment or placebo at a ratio of 2:1 per cohort. Subjects will be blinded to study treatment while physicians will not be blinded.

The study will be composed of 2 treatment cohorts, 12 subjects at cohort 1 and 16 subjects at cohort 2.

A total of 28 subjects will be treated in 2 clinical sites.

At cohort 1, a total of 12 subjects will be randomized to receive active or placebo treatment (2:1) according to randomization program that will be prepared prior to study initiation. At cohort 2, 16 subjects will be randomized to receive active or placebo treatment. Each clinical site will have at least one active and one placebo treatment subject per each study cohort. In case of slow enrollment in one of the sites, other sites may complete the enrollment of subjects in each cohort.

3.2. DOSE RATIONALE

In all previous clinical trials, the maximal RZL-012 dose per injection site was 5 mg, and a distance of 2-3 cm or 1 cm between injection points was maintained. The total overall RZL-012 dose tested to date was 180 mg, which is 75% of the NOAEL. No serious adverse events were associated with this dose per injection site, with the distance maintained between injection sites or with the maximal overall dose.

Thus, for the current trial, the starting dose of a maximal 120 mg has been chosen based on a dose of 2.5 mg per injection site, a distance of 1 cm between injection columns and rows of the submental pattern and on an estimation of the dimensions of the submental area. A distance of 1 cm will allow a good distribution RZL-012 into the submental area.

To increase the potential to demonstrate efficacy, a higher RZL-012 dose of a maximal 240 mg will also be assessed, on condition that no serious safety concerns are raised within 28 days of follow-up post-dose of 12 subjects having received the starting dose. To achieve this maximal dose, the 5 mg dose per injection site will be used with the same pattern of submental fat grid (i.e., 1 cm between injection columns and 1 cm between injection rows). The number of injections will be determined by the physician based on the fullness of submental fat. Upon review of initial safety data in subjects receiving the lower dose, sponsor may or may not decide to increase the dose as planned for remaining subjects.

3.3. DOSING

3.3.1. Dosing Regimen

All subjects will receive a single dose of RZL-012 or placebo in multiple injections, in accordance with the treatment cohorts as shown in Table 2 below.

Table 2: Study Design

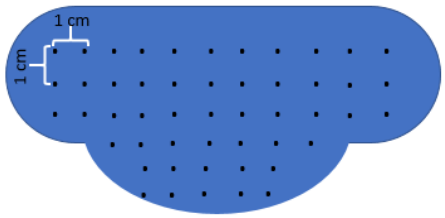
	N=28	
	Cohort 1 N=12	Cohort 2 N=16
Number of RZL-012/Placebo	8/4	At least 4 placebo subjects
Total Maximal Dose RZL-012 (mg)/vehicle (mL)	Up to 120 mg/2.4 mL	Up to 240 mg/4.8 mL
Dose of RZL-012 (mg)/vehicle (mL) per single injection	2.5 mg/0.05 mL	5 mg/0.1 mL
Maximal Number of Injections per subject	48	48

Cohort 1 active subjects will receive a maximal dose of up to 120 mg RZL-012 in a series of up to 48 injections. Each injection point will be dosed with 2.5 mg RZL-012 (0.05 mL of RZL-012 solution). Placebo (vehicle) subjects will be injected with 0.05 mL vehicle at each injection site, resulting in a total volume of up to 2.4 mL.

Cohort 2 active subjects will receive a maximal dose of up to 240 mg RZL-012 in a series of up to 48 injections. Each injection point will be dosed with 5 mg RZL-012 (0.1 mL of RZL-012 solution). Placebo (vehicle) subjects will be injected with 0.1 mL vehicle at each injection site, resulting in a total volume of up to 4.8 mL.

The injection pattern in Cohort 1 and Cohort 2 will be based on a submental area shaped grid in which the distance between rows will be 1cm and distance between columns will also be 1 cm as seen in the figure below. Physician will choose two points at the edge of the 50-point pattern that will not be injected (up to 48 injections):

Figure 5: Scheme of Injection Pattern that will be used by the Physician to Inject into the Submental Fat Area in Both Study Cohorts



Twelve (12) subjects from Cohort 1 that will be enrolled in 2 clinical sites (8 active and 4 placebo) will be injected with a maximal dose of 120 mg/subject or with up to 2.4 mL of vehicle. If no serious safety concerns will be noted within 28 days of follow-up post-dose of subjects from Cohort 1, the study will proceed to the additional 16 subjects of Cohort 2. These subjects (that will be randomized to receive active or placebo treatment with at least 4 placebo subjects) will be injected with a maximal dose of 240 mg/subjector up to 4.8 mL vehicle .

Treatment of Cohort 2 will start following Cohort 1 Day 28 data. An independent Data Safety Monitoring Board (DSMB) will review the safety and tolerability data for Cohort 1 subjects, 28 days after injection, and decide whether it is safe to increase the dose for next study cohort. The decision to proceed to the Cohort 2 will be made within 30 days (28 days +2) after injection of the last dosed subject of Cohort 1.

The DSMB will be comprised of 2 independent MDs with expertise in the aesthetic area and in conduction of clinical trials.

In case of serious safety concerns (e.g., prolonged severe swelling or severe pain following injection) among Cohort 1 subjects receiving the 120 mg dose, sponsor and DSMB may decide to reduce or stay with the 120 mg/subject dose level for Cohort 2 subjects.

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

3.3.2. Serious Adverse Events Considered Related to the Investigational Drug

The adverse events (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 possibly or probably 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.

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINTS

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

In cohort 1a total of 12 subjects will be randomized to receive active treatment or placebo (2:1) and in cohort 2 16 subjects will be randomized (at least 4 placebo subjects will be randomized) in the 2 clinical sites. Each clinical site will have at least one active and one placebo at each study cohort.

Twelve (12) subjects from Cohort 1 (8 active and 4 placebo) will be injected with a maximal dose of 120mg/subject or with up to 2.4 mL of vehicle. If no serious safety concerns will be noted within 28 days of follow-up post-dose of subjects from Cohort 1 (e.g., prolonged severe pain or severe swelling following injection), the study will proceed to the additional 16 subjects of Cohort 2 that are designated to be injected with a maximal dose of 240 mg/subject for active treatment or up to 4.8 mL vehicle in 4 for at least 4 placebo subjects that will b randomized.

In case of serious safety concerns among subjects receiving the 120 mg dose, sponsor and DSMB review may decide to reduce or remain with the 120 mg/subject dose level for remaining subjects.

4.2. SECONDARY ENDPOINTS

Following are the study's secondary endpoints that evaluate treatment efficacy of active treatment vs. placebo subjects:

1. Improvement of Physician' global assessment questionnaire for treatment efficacy in active vs. placebo treated subjects on Days 28, 56, and 84 follow up visits to evaluate treatment response, see definition in Section 6.1.15.2.1.

2. Reduction from baseline in submental fat volume, as measured with MRI on Day 84 vs. screening, in RZL-012 treated subjects vs. placebo treated subjects, see definition in Section 6.1.15.2.2.

3. Improvement from baseline in Subject's satisfaction Rating by using validated FACE-Q questionnaire (Satisfaction of chin) on Days 28, 56, and 84 follow up visits to evaluate treatment response among RZL-012 treated subjects vs. placebo treated subjects, see definition in Section 6.1.15.2.3.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

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

1. Men and women 18-65 years old, all in good health.
2. Subjects with Body Mass Index < 35 as determined at screening visit.
3. Subjects must have submental skin fold thickness greater than 1.5 cm as measured with calipers.
4. Males must be willing to be clean shaved for all study visits.
5. Patient weight must be stable (no fluctuation of >15 pounds in the past year).
6. Males or females in the age of fertility agree to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012.
7. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study.
8. Subjects must sign an IRB approved informed consent indicating they are aware of the investigational nature of the study.

5.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded:

1. Unable to tolerate subcutaneous injection.
2. Pregnant or lactating women.
3. Subjects with dysfunctional gallbladder activity, e.g., underwent cholecystectomy or cholecystitis.
4. Any uncontrolled systemic disease -a potential patient in whom therapy for a systemic disease is not yet stabilized will not be considered for entry into the study.
5. Treatment with botulinum toxin injections in the neck or chin area within 6 months before screening.
6. Excessive submental skin laxity.
7. Any Scars, unshaven hair, tattoos or jewelry on or near the proposed treatment area.
8. Significant history or current evidence of a medical, psychological or other disorder that, in the investigator's opinion, would preclude enrollment into the study.

9. An active dermatitis or open wound in the proposed treatment area.
10. An active bacterial, fungal, or viral infection in the proposed treatment area.
11. Pre-existing skin condition to the submental region that may confound evaluation or analysis, at investigator discretion.
12. Previously treated with focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate to the submental region within the previous 6 months.
13. Pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia or facial nerve palsy.
14. Pre-existing medical condition other than increased submental fat that may result in increased submental fullness such as but not limited to thyroid enlargement, goiter, cervical lymphadenopathy etc., at investigator discretion.
15. Must not have a planned fat reduction procedure of any variety to the submental region for the duration of the study.
16. Must not have planned significant alterations in diet or physical activity that may result in significant fluctuations in weight.
17. Subjects with medication or history of coagulopathy.
18. Allergic subjects to Benadryl.
19. Subjects treated chronically at least 3 months prior to study entry with systemic steroids or immunosuppressive drugs.
20. Subjects treated chronically at least one week prior to study entry with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
21. Current participation or participation within 3 months prior to the start of this study in a drug or other investigational research study.
22. Claustrophobia or MRI incompatible device or implant.

5.3. SUBJECT IDENTIFICATION

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

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

Subjects experiencing serious side effect will be withdrawn from the study, but 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.

6. STUDY PROCEDURES AND ASSESSMENT

6.1. DEFINITIONS OF STUDY PROCEDURES

6.1.1. Informed Consent

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

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

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

If a subject is unable to read, he may not participate in the study.

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

The investigator should document in the source data that the Informed Consent was signed prior to subject's participation in the study and according to the International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, as described above.

6.1.2. Medical History

Subjects' medical history should be fully documented at Screening Day (45 through 1 day prior to baseline), to ensure compliance with study inclusion criteria and the absence of circumstance mentioned in the exclusion criteria. Medical history information must include, but not be limited

to, past and present medical conditions, concomitant non-drug treatments and hypersensitivity to drugs.

6.1.3. Concomitant Medication

All concomitant medication given 1 month prior to study entry, including blood and blood products, dietary supplements, and non-prescription drugs will be listed at screening/baseline. Each entry will include the treatment's start date, treatment name (Generic), reason for use, dosing regimen (dose and frequency of use), route of administration, and stop date (if applicable). The clinical significance of the medication use will be decided by the investigator. Study subjects will be routinely questioned for changes in the administration of concomitant medication during the trial and changes should be updated from medical records as well.

6.1.4. Physical Examination

The investigator (or medically qualified nominee) will conduct a complete physical examination, at Screening Day (performed 45 through 1 days prior to baseline). Additional examination that will be performed during screening will include height and weight measurements to determine BMI in order to ensure compliance with study criteria. 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 6 categories of skins 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 a 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

6.1.5. Weight Measurement

Weight measurement will be performed at screening visit to determine BMI value prior to injection. An additional weight measurement will be performed at Baseline visit and on study visits at Day 56 and 84 following injection to verify that there are no significant changes in weight throughout the assessment of submental fat changes during the study.

6.1.6. Vital Signs Measurements

Subjects' vital signs will be measured at Screening Day (performed 45 through 1 days prior to baseline) in order to ensure compliance with study inclusion criteria.

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

Additional vital signs measurements to assess subject's safety will be performed at baseline visit (Day 0) prior to drug injection, the following day (Day 1) after drug injection and on study visits 7, 14, 28, and 56 days following injection.

6.1.7. Draize Score

Subjects' skin irritancy will be evaluated by Draize score at baseline visit prior to injection in order to establish a baseline to compare following drug injection.

Additional skin irritancy evaluation to assess subject's safety will be performed at baseline visit 2 hours ± 30min following injection, on the following visits days: 1, 7,14, 28, 56, and 84.

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

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

6.1.8. 2D Standardized Photography

Standardized photography (2 dimensional) of the face (submental fat area) will be applied at baseline visit prior to treatment in order to establish a baseline to compare following drug injection.

Additional photography will be conducted on Days: 7, 14, 28, 56, and 84 to evaluate qualitative changes in submental fat area at study follow ups and to assist physician and subjects to assess treatment efficacy and satisfaction by comparison of images taken at each study visit vs. screening visit.

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

Lateral and anterior images of the face will be taken.

6.1.9. MRI

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

MRI will be conducted to all subjects enrolled into the study, at Screening Day (performed 45 through 1 day prior to baseline) in order to establish a baseline to compare at study endpoint, and at Day 84.

MRI (performed during screening period) will be conducted after subject qualifies on all screening criteria within a window of 5 days from the visit in the clinic. Post-treatment period MRI will be completed 84 days (± 5 days) after the subject's last treatment session.

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

Sagittal 2D and 3D images of the head and neck (chin area) will be obtained using 1.5 Tesla machine (General Electric or Siemens or Phillips). For each MRI acquisition visit, the total imaging time is expected to be approximately 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 submental fat 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. MRI will be performed according to a detailed written manual.

Images should be saved in a DICOM format with the information of date and subject's screening number to be transferred by the Sponsor's request for central analysis.

Submental volume analysis will be performed by computer-assisted tools to delineate the tissue boundaries and limits of the submental region and calculation of submental volume will be done before and following RZL-012 injection.

6.1.10. Subject's Satisfaction Rating following Treatment

Subject's satisfaction questionnaire will be collected by use of FACE-Q questionnaire (Copyright©2013 Memorial Sloan-Kettering Cancer Center, New York, USA), at baseline visit prior to injection and at posttreatment follow up visits Day 28, 56, and 84.

The questionnaire will be filled following a comparison of 2D images taken at each time point and comparison to the images taken at baseline visit, prior to injection of RZL-012

The comparison of the images at each study visit vs. baseline will be done by displaying the images of the images of the visit day vs. baseline on the computer.

The FACE-Q questionnaire includes a list of 10 questions related to the chin visibility and degree of subject's satisfaction from his/her chin at each question. Some of the scores reflect a better outcome. A Conversion Table to convert the raw scale summed score into a score from 0 (worst) to 100 (best). See Appendix III for conversion table of FACE-Q questionnaire.

The list of the questions of Face-Q questionnaire is described below:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The style of your chin (e.g. masculine or feminine)?	1	2	3	4
b. The size of your chin?	1	2	3	4
c. The width of your chin?	1	2	3	4
d. How well your chin suits your face?	1	2	3	4
e. How sculpted your chin looks (e.g. well defined)?	1	2	3	4
f. The shape of your chin?	1	2	3	4
g. How your chin looks in profile (side view)?	1	2	3	4
h. How your chin looks in photos?	1	2	3	4
i. How your chin projects compared to the rest of your face?	1	2	3	4
j. How your chin looks from every angle?	1	2	3	4

6.1.11. Physician's Evaluation of Improvement

Physician evaluation of improvement will be conducted by using physician's global assessment of submental fat at posttreatment follow-up visits, Days 28, 56, and 84 following injections.

The evaluation will be made by the physician and based on comparison of the submental fat area of the subject at each visit time point to the 2D images that were taken at baseline visit, prior to injection of RZL-012.

The assessment will grade the improvement in submental fat condition at each follow up time point Day 28, 56 and 84 vs. Baseline:

Grade		Description
0	Completely clear	No evidence of submental fat volume; 100% improvement
1	Almost clear	Very significant clearance (≥90% to <100%); only trace remain
2	Marked improvement	Significant improvement (≥75% to <90%); some evidence of submental fat remains
3	Moderate improvement	Intermediate between slight and marked improvement (≥50% to <75%)
4	Slight improvement	Some improvement (≥25% to <50%); significance evidence of submental fat remains
5	No change	Submental fat has not changed from baseline condition (±25%)
6	Worse	Submental fat is worse than at baseline evaluation by ≥25% or more

6.1.12. Pregnancy Test

Pregnancy test will be performed by women in the age of fertility to eliminate pregnancy prior to dosing at Baseline visit.

At screening visit women will be asked whether they are pregnant, as part of exclusion criteria.

6.1.13. Submental Fat Thickness using Calipers

Prior to study entry, at screening visit, 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.

Only subjects with skin fold larger than 1.5 cm will be enrolled into the study.

6.1.14. Adverse Events

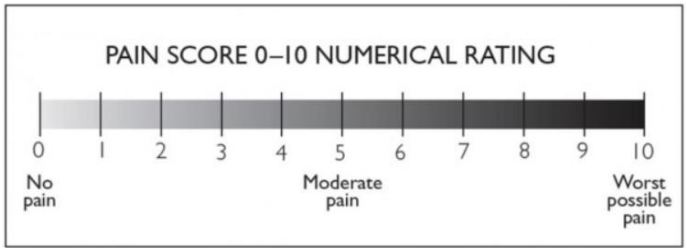
The information obtained via subjects questioning through the study visits, review of subject's compliance record, evaluation of skin irritancy, vital signs measurements, and by any other means will be evaluated in light of baseline medical data and thus provide the basis for adverse events identification and grading.

Twelve (12) subjects from cohort 1 (8 active and 4 placebo) will be injected with a maximal dose of 120 mg/subject or with up to 2.4 mL of vehicle. If no serious safety concerns will be noted within 28 days of follow-up post-dose of subjects from cohort 1, the study will proceed to the additional 16 subjects of cohort 2 that are designated to be injected with a maximal dose of 240mg/subject for active treatment or up to 4.8 mL vehicle in at least 4 placebo subjects that will be randomized.

The AEs reported during the trial will be graded (see Section 9), documented, and assessed in light of their clinical significance and relation to investigational product. Specifically, the tolerability and assessment of the AEs related to skin condition and injection procedure will be monitored among RZL-012 vs. placebo treated subjects: bruising, pain, induration erythema, and swelling/edema.

Erythema and Edema will be assessed according to Draize Score, as described in Section 6.1.7.

Pain will be assessed by using Numeric Rating Scale (NRS). NRS is an 11-point scale for patient self-reporting of pain, where 0 is no pain, rate 1-3 is mild pain, rate 4-6 is moderate pain and rate of 7-10 is severe pain, where 10 is worst pain imaginable.



Induration will be assessed by palpation of submental fat area.

Bruising will be assessed by visual inspection.

Individual 4-point grading scales were implemented to provide greater specificity in the characterization of bruising and induration (4).

Table 3: Grading scales of bruising and induration

Grade	Bruising	Induration
0	No Bruising	No Induration
1	Bruising associated with 1–3 needle insertion points	Induration associated with at least approximately 30% of the treatment area
2	Bruising spreading beyond 4 or more individual needle insertion points but contained within the treatment area	Induration associated with greater than approximately 30% to at least 60% of the treatment area
3	Bruising covering the entire treatment area but contained within it	Induration covering the entire treatment area but contained within it
4	Bruising of the neck and face beyond the treatment area	Induration of the neck and face beyond the treatment area

In addition, the following information regarding AEs must be obtained: AE description, start date, end date (if applicable) or ongoing, severity, seriousness, relationship to study drug, outcome (e.g., resolved / unresolved), and action taken (e.g., concomitant medication). The sponsor or the sponsor representative will provide information regarding serious adverse event (SAE) expectedness based on data included in the IB. AE monitoring will be conducted throughout subject's participation up to 84 days after injection.

6.1.15. Evaluation of Response

Evaluation of response will be conducted on Days 28, 56, and 84 following injection.

6.1.15.1. Evaluation of Primary Endpoints

6.1.15.1.1. Safety and Tolerability Monitoring

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

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

1. AEs related to skin condition and injection procedure, general AEs and SAEs, including severity, relation to study treatment and classification by whether or not these events comprise intolerable side effects.
2. Physical exams, Draize score and vital signs measurements.
3. Subjects questioning - full medical history during screening, routine AE reporting.

6.1.15.2. Evaluation of Secondary Endpoints

6.1.15.2.1. Physician evaluation of treatment

Evaluation of treatment response by physician and obtaining a low score among RZL-012 treated subjects vs. placebo treated subjects, as measured by a 7 grade scale. This will be conducted on Days 28, 56, and 84 follow up visits.

6.1.15.2.2. MRI to calculate volume changes of submental fat

MRI will be conducted at Screening Visit and on Day 84 visits to quantitively assess a change or reduction from baseline in submental fat dimensions (volumetric measurement).

MRI (performed during screening period) will be conducted after subject qualifies on all screening criteria within a window of 5 days from the visit in the clinic. Post-treatment period MRI will be completed 84 days (± 5 days) after the subject's last treatment session.

Lower volume is expected to be measured 84 days following treatment among RZL-012 treated subjects and no change or minor change in submental fat volume is expected in placebo treated subjects. This will be served as an objective parameter to asses treatment efficacy.

6.1.15.2.3. Subject's Satisfaction Questionnaire at earlier timepoints than study termination

Evaluation of subject's treatment satisfaction by using the Face-Q satisfaction questionnaire rating score at each of the follow ups visit compared to baseline. The evaluation will be conducted at baseline visit and on Day 28, 56, and 84 following injection. A higher grade following the use of conversion table of the questionnaire is expected among RZL-012 treated subjects compared placebo at follow ups visits vs. baseline.

6.1.15.3. Compliance Monitoring

Compliance monitoring will include the following procedures:

- Compliance assessment by site coordinator at the study visit, including but not limited to subject questioning.

6.1.15.4. Dispensing of RZL-012 Investigational Product

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

6.1.15.5. Questioning of Study Subjects

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

6.2. STUDY VISITS

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

6.2.1. Screening Procedures

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

Screening visit should be performed 45 days ahead and no later than 1 day prior to baseline visit for the two study cohorts.

Study Screening Day procedures will include the following:

- Informed Consent - Section 6.1.1
- Medical History - Section 6.1.2
- Concomitant Medication - Section 6.1.3
- Physical Examination - Section 6.1.4
- Weight Measurement – Section 6.1.5
- Vital signs Measurement –Section 6.1.6
- MRI – Section 6.1.9
- Pregnancy elimination – Section 6.1.12
- Caliper measurement of submental fat thickness – Section 6.1.13

Subjects may be rescreened if they were screened and not dosed within 45 days. The following procedures will be performed: vital signs, weight measurements.

6.2.2. Study Randomization

Subjects will be randomized to each study group, i.e., investigational therapy or control, according to a predefined randomization scheme in a ratio of 2:1 (active:placebo) among the

2 clinical sites and per each study cohort. The investigational therapy group will be treated with RZL-012 and the control group will be treated with the same formulation (vehicle) as with RZL-012, absent active medication.

Assignment to study group will be disclosed only after subject eligibility is confirmed and immediately before treatment initiation. The investigator and clinical staff will be unmasked and will be responsible to fill the syringes for injection. The subject will be blinded and will not know whether he is injected with active or placebo treatment.

6.2.3. Study Treatment

6.2.3.1. Treatment with RZL-012 Investigational Drug to Submental Fat

RZL-012 or placebo is an investigational product supplied as a single treatment in multiple sites of injections (48 injections).

The injection dosing regimen and technique is crucial for the therapy safety.

The following procedures prior to injection into the submental fat 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 RZL-012 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, where the printed grid pattern facing the skin. The grid paper backing will be thoroughly wetted with a cotton pad soaked with sterile water. Following 15 seconds waiting, the grid cover will be peeled off.

5. The number of injections and injection volume in each cohort will be determined following physician's evaluation.

6. Syringes will be filled with 0.5 mL (Cohort 1) or 1 mL (Cohort 2) RZL-012 or vehicle and the number of syringes will be compatible with the total volume of injection. Up to 5 syringes for a total volume of 2.4 mL (each syringe having a volume of 0.5 mL) or up to 5 syringes (each syringe having a volume of 1 mL) for a total volume of 4.8 mL. See table below for details on injection of both cohorts:

Cohort	Syringe volume	Injection volume of RZL-012/placebo	No. of injections	Total injected volume of RZL-012 or placebo	Amount of injected RZL-012
1	0.5 ml	0.05 ml	Up to 48	Up to 2.4 mL	Up to 120 mg
2	1 ml	0.1 ml	Up to 48	Up to 4.8 mL	Up to 240 mg

7. All injections will be administered diagonally in 90°, using a 0.5 mL syringe (Cohort 1) or 1 mL (Cohort 2) Luer-lock syringe and a 29/30 G 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 before injecting to ensure that no blood is coming out. If so, the plunger should be pushed down to inject the medicine. The formulation is viscous; therefore, a resistance is expected while injecting.

9. Immediately following completion injection of the submental fat, an ice/cold pack will be applied for immediate pain relief. It will be held by the subject for at least 2 minutes.

10. The physician will record the number of injections administrated for each subject, at each cohort.

In Cohort 1, the first 8 subjects randomly assigned to the RZL-012 treatment group will initiate at the dose of 2.5 mg (0.05 mL volume of RZL-012 solution) RZL-012 in a single injection (resulting in a total of up to 120 mg) in a series of maximum 48 injections. Additional 4 subjects will be given placebo (vehicle) in a volume of 0.05 mL in a single injection, resulting in a maximal volume of 2.4 mL injected into the submental area.

In Cohort 2, an additional 16 subjects randomly assigned to the RZL-012 treatment group will initiate at the dose of 5 mg (0.1 mL volume of RZL-012 solution) RZL-012 in a single injection (resulting in a total of up to 240 mg) in a series of maximum 48 injections, where at least 4 subjects will be given placebo (vehicle) in a volume of 0.1 mL in a single injection, resulting in a maximal volume of 4.8 mL.

The injection pattern that will be used in both cohorts will be based on existing grid in the shape of submental area, where distance between injection rows will be 1cm and distance between injection columns will be 1cm as seen in Figure 5, Section 3.3.1.

The amount of injections for each subject will be decided by the physician according to the fullness of submental fat.

In cases where the physician will have to inject a total number of 48 injections, the physician will choose two points in the edge of the grid pattern that will not be injected (The grid contains 50 injections points).

If no serious safety concerns will be noted by DSMB within 28 days of follow-up post-dose of subjects from Cohort 1, the study will proceed to cohort 2 where an additional 16 subjects will receive active treatment where at least 4 out of the 16 subjects will be injected with vehicle.

Each RZL-012 kit contains 1 vial (250 mg/5 mL) corresponding to the number of subjects receiving treatment in each cohort.

RZL-012 will be injected on Day 0 study visit (baseline).

Following completion of injections, an ice pack will be placed on the injected area for pain relief. Subject will have to remain seated in the injection position for an additional 10 minutes after dosing. Following completion of injection procedures, subjects will remain in the clinic for an additional 2 hours±30min for medical supervision and in order to follow adverse events following injection. During the stay in the clinic there are no restrictions in terms of activity or diet.

6.2.4. Treatment with Placebo

Four (4) subjects randomly assigned to the study in every cohort will be injected placebo, which will be a vehicle control (tween-80, propylene glycol, benzyl alcohol and water) in the same manner as mentioned above (Section 6.2.3.1).

6.2.5. Baseline Visit

Baseline visit is defined in the study as Day 0. Baseline visit will be performed to complete screening evaluation, and to review all procedures necessary to confirm subject eligibility. Subjects will stay under supervision in the study center till 2 hours ± 30 minutes following drug injection.

Screening information may be considered for baseline data if acquired within the adequate timeframe as described in Table 4.

Table 4: Subject Information and Timeframes

Information	Timeframe	Follow-up Timeframe
Informed Consent Form	Signed prior to any study dedicated procedure	
Medical History	At Screening Day visit	
RZL-012 dosing	At baseline	
Concomitant Medications	At screening Day visit and at baseline, Day 1, 7, 14, 28, 56, and 84	
Physical examination	At Screening Day visit	
Weight measurement	At screening visit, baseline, day 56 and 84	
Vital Signs	At Screening Day visit and at Days 0, 1, 7, 14, 21, 28 and 56	
Pregnancy test (women only)	Will be performed at Baseline	
Caliper measurement of submental thickness	Will be performed at Screening day	
Subject's satisfaction questionnaire (FACE-Q)	At baseline and at Days 28, 56	Day 84
Physician evaluation of treatment using Physician's global assessment questionnaire	At Day 28 and 56	Day 84
MRI	At Screening	Day 84
Photography of submental fat 2D	At Baseline, Day 7,14,28	On 56 and 84
Draize Score at the Injected Site	At Baseline visit (pre- and following injection) and on Day 1, 7, 14, 28, 56	Day 84
AE Assessment for submental fat skin area (pain, bruising and induration grading) and general AEs	At Days 0 (pre- and following injection), 1 7, 14, 28, 56	Day 84

6.2.6. Subject Site Visits

Subject site visits will be performed ± 1 day from scheduled date (for study visits at Days 7, 14, 28, 56, and 84).

For site visit that results in study discontinuation, see termination visit in Section 6.2.7.

6.2.7. Termination Visit

Once study is discontinued, all reasonable measures should be taken to perform a termination visit. Termination visit should include all procedures necessary to complete subjects' records:

AE reporting, evaluation of response and updating of subject contact information. An effort should be made to perform all activities conducted on visit Day 84.

6.2.8. Unscheduled Visit

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

7. SAFETY CONSIDERATIONS AND GUIDANCE FOR INVESTIGATORS

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

7.1. STUDY RESTRICTIONS REGARDING CONCOMITANT MEDICATIONS

Subjects may not receive the following medications at least 3 months prior to study entry:

- Chronic treatment with systemic steroids or immunosuppressive drugs.
- Any investigational product other than RZL-012.

Subjects may not receive the following medications at least one week prior to study entry:

- Chronic treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Before dosing, topical analgesic gels such as Lidocaine (e.g., Emla) or Pramoxine may be used to numb the injected site. An ice pack should be applied on the site of injection immediately following dosing to help reduce pain.

At Day 1 following injection application of the antihistamine Benadryl Gel (Diphenhydramine hydrochloride 1% for topical use only) may be initiated prophylactically, according to drug instructions for use, to avoid itching at the injected area. Benadryl Gel should be applied for 7 days or as needed.

7.2. SAFETY MEASUREMENTS

Safety measurements will be performed by monitoring the specific skin AEs: bruising, pain, induration, erythema and swelling/edema that have been identified as being associated with the use of RZL-012 investigational product. The AEs of RZL-012 vs. placebo will be evaluated for their frequency, severity and duration.

7.3. PREMATURE DISCONTINUATION FROM STUDY

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

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

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

7.4. PREMATURE STUDY TERMINATION

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

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

7.5. DEVIATION FROM STUDY PROTOCOL

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

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

Any other changes to or deviations from the protocol will be made as an amendment to the protocol and must be approved by the Sponsor or its official designee and the local IRB/EC

before they can be implemented. Accordingly, the Sponsor will not assume responsibility or liability for any unauthorized deviation from or change to the protocol.

8. INVESTIGATIONAL PRODUCT AND VEHICLE SPECIFICATIONS

8.1. DESCRIPTION OF RZL-012

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

8.2. FORMULATION, PACKAGING AND LABELING

The RZL-012 drug is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 250 mg/5 mL RZL-012 in formulation F12.

The vehicle is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 5 mL of formulation F12.

8.3. STORAGE AND STABILITY OF RZL-012 AND VEHICLE

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

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

The storage conditions are summarized in Table 5.

Table 5: RZL-012 Storage Conditions

Storage Conditions	Maximal Storage Duration
Individual vials: Room temperature (15-30 °C)	According to expiration date as will be provided by manufacturer.
* Drug product stability program has successfully reached 3 years.	

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

8.4.1. Dosage

RZL-012 therapy is available in vials of 250 mg/5 mL.

The vehicle is available in vials of 5 mL.

8.4.2. Administration and Instructions for Use

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

The vial should be manually shaken before consumption.

1 mL Luer-lock syringe or 0.5mL syringe with RZL-012 solution should be filled with 30/29 G 1/2" sterile needle as described below:

- Cohort 1 – a maximal dose of 120 mg:

  A maximum of 48* 0.05 mL/ subject results in filling of up to 5 syringes in the volume of 0.5mL, prior to injection.

- Cohort 2 – a maximal dose of 240 mg:

  A maximum of 48* 0.1 mL/ subject results in filling of up to 5 syringes in the volume of 1 mL, prior to injection.

One vial will be used for dosing of one subject. Breached vials will not be re-used for other subjects. Each vial must be placed back into the container. All open vials must be kept until the end of the study for the Sponsor to decide either to discard or return to the Sponsor.

8.5. ACCOUNTABILITY OF RZL-012 AND VEHICLE

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

The vehicle was manufactured and packed by Nextar (Israel) and complies with cGMP requirements.

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

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

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

9. ADVERSE EVENTS

9.1. ADVERSE EVENT DEFINITIONS

9.1.1. Definition of AE

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

9.1.2. Definition of Serious Adverse Event

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

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

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

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

9.1.3. Definition of Adverse Drug Reaction

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

9.2. ADVERSE EVENT GRADING

AE will be documented in each study visit.

AEs severity will be graded as follows:

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

9.3. CAUSALITY ASSESSMENT OF ADVERSE EVENTS

All AEs will be evaluated by the investigator and assigned an estimated relationship to the RZL-012 investigational product. The terms "related" or "unrelated" refer to the association with the use of the investigational product, as defined below in Table 6.

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

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

Definition of AEs causality is specified in the table below (Table 6).

Table 6: Definition of Causality

TERM	DEFINITION	CLARIFICATION
Unrelated	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)	
		▪
		▪
		▪
Related	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with high degree of certainty to be related to the study procedures/investigational product.	An AE may be considered related if or when all of the following apply: ▪ It follows a reasonable temporal sequence from study procedures/administration of the investigational product. ▪ It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject. ▪ It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the investigational product, yet investigational product-relatedness clearly exists. ▪ It follows a known pattern of response to the study procedures/investigational product.

9.4. UNEXPECTEDNESS OF ADVERSE DRUG REACTIONS

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

9.5. ADVERSE EVENT REPORTING AND MONITORING REQUIREMENTS

9.5.1. General

All AEs, serious and non-serious, will be fully documented in both source documents and CRFs as described in Section 6.1.14, and each AE will be assessed in light of its clinical significance. For each AE, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship to the investigational drug, i.e., causality assessment, for each AE.

Any AE occurring prior to initiation of first dose, after initiation of the first dose and or during any point throughout the study should be recorded on the AE page of the CRF. All AEs occurring until subject is terminated from the study (84 days after the injection of RZL-012), should be captured in the CRF. AEs should be recorded in the CRF using the medical

terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

Occurrence of any serious or severe ADR must warrant clinical evaluation by the treating investigator and reported to the Sponsor/medical monitor within 24 hours.

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

9.5.2. SAE Reporting

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

Sponsor contact details for SAE reporting:

Dr. Sarina Tanimoto, RazielSafety@pacificlinkconsulting.com or fax: 858-769-0288.

An initial report must be faxed or emailed to RazielSafety@pacificlinkconsulting.com fax: 858-769-0288 within 24 hours of becoming aware of the event and must include SAE general description, start date, end date (if applicable), the reason for evaluation as a SAE, basic subject information, assessment of the relationship to the investigational product, expectedness, and study therapy information.

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

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

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

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

9.5.3. Expedited Reporting

Expedited reporting by PI to IRB/EC is warranted for all Suspected Unexpected Serious Adverse Reactions (SUSAR), i.e., unexpected SAEs that are considered related to study product as

defined in Sections 9.1.2, 9.1.3, and 9.4). Additional cases will be communicated by PI to IRB/EC via expedited reporting when required by local regulation.

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

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

10. STATISTICAL CONSIDERATIONS

10.1. STUDY DESIGN AND OBJECTIVE

This study is planned as a single blind, randomized, placebo-controlled, Phase 2a, 2-cohort study for the treatment of submental fat. Eligible subjects will be randomized to receive either RZL-012 or placebo (vehicle) in each study cohort and will be monitored for safety and efficacy during 84 days of follow up.

Primary objective:

The main objective is to evaluate safety following injection of RZL-012 vs. placebo into submental fat. Skin irritancy and AEs related to the injection procedure will be evaluated for frequency, severity and duration. Specifically, tolerability and assessment of the following AEs will be monitored: bruising, pain, induration erythema and swelling/edema.

Secondary Endpoints:

Secondary endpoints will test the efficacy of RZL-012 vs. placebo according to the following measures:

1. Improvement of Physician's global assessment questionnaire for treatment efficacy in active vs. placebo treated subjects at Day 28, 56 and 84 following injection.

2. Reduction from baseline in submental fat volume as measured by MRI, in RZL-012 treated subjects vs. placebo treated subjects at Day 84 following injection.

3. Improvement from baseline in the self-assessment of submental fat using the Face-Q satisfaction questionnaire rating score in RZL-012 treated subjects vs. placebo treated subjects on Days 28, 56 and 84.

10.2. STUDY ENDPOINTS

10.2.1. Primary Safety Endpoints

Skin AEs will be evaluated for their frequency, severity and duration. Specifically, the assessment of the following AEs will be monitored among RZL-012 vs. placebo treated subjects: bruising, pain, induration, erythema, and swelling/edema.

10.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include testing of RZL-012 vs. placebo according to the following measures:

- Improvement in Physician's global assessment questionnaire for treatment efficacy assessment at Day 28, 56, and 84 following injection.
- Improvement from baseline in a quantitative measure of submental volume as measured by MRI, before and 3 months after injection.

  Improvement from baseline in score of FACE-Q questionnaire rating subject's satisfaction on Day 28, 56, and 84 follow up visits.

10.2.3. Safety and Tolerability Endpoints

Safety endpoints include:

- Incidence of AEs and SAEs, by severity and relation to study treatment of RZL-012 vs. placebo treated subjects. AEs will be coded using MedDRA version 22 (or higher).
- Specific AEs will be closely monitored: bruising, pain, induration and swelling/ Edema and Erythema (Draize Score).
- Vital signs

10.3. SAMPLE SIZE JUSTIFICATION

A maximum of 28 evaluable subjects will be included in the study (12 cohort 1 and 16 in cohort 2) and followed for as long as 3 months.

This study is planned as a dose escalation study following randomization of 8 subjects per active dose group paradigm with the addition of a 4 subjects vehicle control group at cohort 1 (active/placebo ration of 2:1). At cohort 2, out of the 16 subjects that will be randomized, at least 4 subjects will receive placebo treatment.

Selection of sample size of 12/16 at each cohort was based on discussions with physicians and is similar in numbers to that encountered in the literature for treatments at this stage of development.

10.4. ANALYSIS SETS

10.4.1. Safety Analysis Set (SA)

The SA will consist of all enrolled subjects who received the study treatment, (exposed population), including subjects prematurely withdrawn.

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

10.4.2. Efficacy Analysis Set (EF)

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

10.4.3. Statistical Analysis of Analysis Sets

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

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

10.5. STATISTICAL ANALYSIS

10.5.1. General

Statistical analyses will be mainly descriptive in nature where study data will be tabulated and summarized using the mean, standard deviation or standard error. The results will be presented overall per cohort and per treatment.

AEs related to injection and Draize scores will be presented in tabular format by visit, cohort and treatment.

Improvement in Global physician's scale score pf RZL-012 treated subjects vs. placebo treated subjects by cohort and overall.

The average change from baseline in submental volume as analyzed from MRI images will be presented in a tabular form by treatment received (RZL-012 / placebo) by cohort and overall.

The average change in Face Q questionnaires score from baseline will be presented in a tabular form by treatment received (RZL-012 / placebo) by cohort and overall.

Any statistical tests will be two-sided. The required significance level (p value) of findings will be equal to or lower than 5%.

10.5.2. Subject Disposition

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

Note that the actual study duration is for a period of maximum 4.5 months, with efficacy analyses being conducted at Day 28, 56, and 84 visits.

10.5.3. Demographic and Baseline Characteristics

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

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

10.5.4. Primary Safety Endpoint

The incidence of SAEs considered related to treatment will be presented overall and by study cohort.

10.5.5. Efficacy Analysis

The change from baseline of submental fat volume will be presented in tabular form by treatment and dose.

The changes from baseline in FACE-Q score as a function of treatment group will be presented in tabular form per treatment group and dosing group.

10.5.6. Safety and Tolerability

Safety analyses will be descriptive in nature.

All reported AEs will be coded to a standard set of terms using MedDRA coding dictionary (V.22 or higher) treatment.

AEs and tolerability data will be presented descriptively by study cohort. AEs will be tabulated by body system, preferred term, seriousness, severity and relation to study drug by cohort.

10.6. HANDLING OF MISSING DATA

No imputation of missing data will be performed.

10.7. INTERIM ANALYSIS

No interim analysis is planned.

11. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

11.1. DATA COLLECTION AND REPORTING

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

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

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

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

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

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

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

11.2. RECORD KEEPING

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

11.3. SOURCE DATA AND SOURCE DOCUMENTS

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

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

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

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

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

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

11.4. STUDY MONITORING

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

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

11.5. CONFIDENTIALITY, DATA DISCLOSURE, AND PUBLICATION

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

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

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

The Sponsor has full ownership of the original CRFs completed as part of the study.

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

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

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

Raziel Therapeutics Ltd. will disclose the results of the trial on the basis of the final analysis and following the revision of a draft manuscript by the investigators, unless posting would compromise publication in a peer-reviewed medical journal or contravene national laws or regulations. Study results may also be disclosed through presentations and abstract submissions at professional scientific meetings.

12. HUMAN SUBJECTS

12.1. DECLARATION OF HELSINKI

Both the PI and the Sponsor will ensure that the study is conducted in agreement with the Declaration of Helsinki, ICH-GCP, and the local laws and regulation.

12.2. INFORMED CONSENT

As described in Section 6.1.1.

12.2.1. LIABILITY AND INSURANCE CONDITIONS

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

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

13. REFERENCES

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

APPENDIX I: TRIAL SCHEDULE OF EVENTS

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					
Study Day[a]	**Day (-45) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 14**	**Day 28**	**Day 56**	**Day 84**
Signed informed consent	X							
Medical history	X							
Physical Exam[b]	X							
Concomitant Medication	X	X	X	X	X	X	X	X
Pregnancy kit test (women)[c]		X						
Caliper measurement of submental fat	X							
Weight measurements	X	X					X	X
Vital signs	X	Pre[d] X post [d]	X	X	X	X	X	
Injection of RZL-012		X						
Physician's global assessment questionnaire						X	X	X
Subject's satisfaction questionnaire (FACE-Q)		X				X	X	X
2D Standardized photography		X		X	X	X	X	X
MRI	X[d]							X
Draize Score		Pre [e] X post [e]	X	X	X	X	X	X
AEs (including pain bruising and induration grading) assessment		X	X	X	X	X	X	X

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

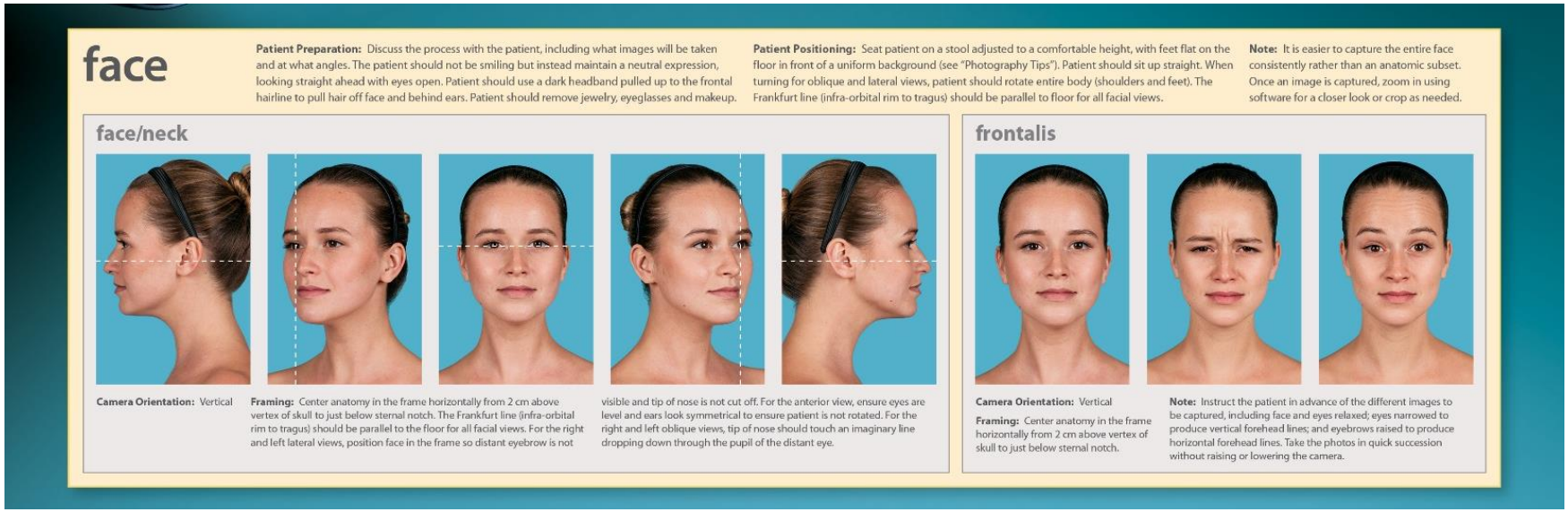
b. Including Fitzpatrick skin type, height, BMI

c. At screening visit women will be asked whether they are pregnant, test will be performed at baseline visit before dosing

d. MRI (performed during screening period) will be conducted after subject qualifies on all screening criteria within a window of 5 days from the visit in the clinic. Post-treatment period MRI will be completed 84 days (± 5 days) after the subject's last treatment session.

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

APPENDIX II: PHOTOGRAPHIC STANDARDS OF THE FACE AREA



APPENDIX III: CONVERSION TABLE FACE-Q QUESTIONNAIRE SUMMED SCORE A SCORE FROM 0 (WORST) TO 100 (BEST)

SUM SCORE	EQUIVALENT RASCH TRANSFORMED SCORE (0-100)
10	0
11	13
12	18
13	22
14	25
15	28
16	30
17	32
18	33
19	35
20	37
21	39
22	40
23	42
24	44
25	46
26	49
27	51
28	54
29	57
30	60
31	63
32	67
33	70
34	73
35	76
36	79
37	83
38	87
39	93
40	100