RAZIEL THERAPEUTICS LTD.

INVESTIGATIONAL NEW DRUG PROTOCOL

RZL-012

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AN OPEN LABEL PHASE 2 STUDY TO EVALUATE THE EFFECTS OF A LOCAL ANESTHETIC, ANTI-INFLAMMATORY MEDICATIONS AND COMPRESSION GARMENTS ON RZL-012-INDUCED ADVERSE EVENTS

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CONFIDENTIAL

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LIST OF ABBREVIATIONS

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

ABBREVIATION	DEFINITION
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MOA	Mechanism of action
MRI	Magnetic resonance imaging
N	Number of subjects
NSAID	Non-steroidal anti-inflammatory drugs
PT	Prothrombin time
PTT	Partial thromboplastin time
RBC	Red blood count
SAE	Serious adverse event
S-CAT	Subject Chin Assessment Tool
SMF	Submental fat
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event(s)
US/USA	United States of America
WBC	White blood cell

STATEMENT OF COMPLIANCE

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

INVESTIGATOR STATEMENT

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

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

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

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

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 8.14.3 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

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

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

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

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

_____	_____	_____
Investigator's Name	Investigator's Signature	Date

1.0 PROTOCOL SUMMARY

1.1 Protocol Synopsis

Study Title	An Open Label Phase 2 Study to Evaluate the Effects of a Local Anesthetic, Anti-inflammatory Medications and Compression Garments on RZL-012-Induced Adverse Events (RZL-012-SMF-SWMTG-P2US-001)
Phase	Phase 2
Study Drug	RZL-012
Study Objectives and Endpoints	Primary Objective: • To compare the benefits of lidocaine, methylprednisolone, Celecoxib +cetirizine or compression dressings on RZL-012-induced adverse events Secondary Objectives: • To test the safety and tolerability profile of combining lidocaine, methylprednisolone, Celecoxib + cetirizine or compression garment with RZL-012 Primary Endpoint: Safety and tolerability profile of combining lidocaine, methylprednisolone , Celecoxib +cetirizine or a compression garment with RZL-012 Exploratory Endpoints: • Proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications. • Proportion of subjects who have at least a 1-grade improvement in the S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications. • Proportion of subjects who have at least a 1-grade improvement in both C-CAT and S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications. • Proportion of subjects who have at least a 2-grade improvement in both C-CAT and S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications. • Changes in SMF volume measured by MRI scans on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications. • Satisfaction in subjects receiving RZL-012 alone or in combination with other medications.
Study Design	This is a Phase 2, open-label, 2-stage, adaptive-design study in which subjects will be randomized into one of 5 treatment groups comprised of RZL-012 with or without additional study treatments: 1. RZL-012 alone 2. RZL-012 and 1% lidocaine with 1:100,000 epinephrine (on Day 1) – 5ml lidocaine will be injected 10 minutes before RZL-012 treatment 3. RZL-012 and oral methylprednisolone dose pack (8 mg (2 tablets) on Day 1 before treatment followed by 16 mg after treatment (as per Instructions for Use)). From Day 2, a daily tapering off by 4 mg until Day 6 will be administered per Rx Instructions for use.

	4. RZL-012 and Celecoxib and cetirizine (200 mg Celecoxib BID and 10 mg cetirizine BID on Days 1, 2, 3, 4, 5 and 6) 5. RZL-012 + sling/pressure garment (until Day 6) In the first stage of the study, 5 subjects will be randomized into each of the treatment groups. Study outcomes will be assessed up to one week thereafter to determine the need to modify additional study treatments. Subsequently up to 10 additional subjects will be randomized into each of the treatment groups for the second stage of the study. For each subject, the study will consist of a screening period, baseline period in which subjects will receive a single treatment session of RZL-012 and a follow-up period. RZL-012 will be administered during a single treatment session via multiple injections into the submental area under the chin. Subjects will thereafter be monitored for safety and efficacy for at least 84 days. Each subject will be treated with the same dose of RZL-012 : • RZL-012 (concentration of injected solution 50 mg/mL RZL-012) of 7.5 mg/0.15 mL/injection point that results in a total dose/volume of 240±30mg mg/4.8±0.6 mL RZL-012, Each subject will receive additional study treatments in accordance with the treatment group to which the subject is randomized. Screening Period: Subjects will undergo screening within 28 days prior to being treated with RZL-012. During the screening period subjects will be assessed for study eligibility by evaluation of subjects' SMF using S-CAT , C-CAT, biochemistry blood tests, MRI, 2D photography. ECG will also be conducted during the screening visit. Following completion of study procedures (including MRI), subjects will be randomized in order for the PI to administer subjects with the Rx prescription, if appropriate (i.e., Celecoxib / cetirizine). Day 1/Baseline: At Baseline visit, subjects will be given with their randomized medication if appropriate. Subjects will receive a single multi-injection treatment of RZL-012 on Day 1. AEs will be recorded. Subjects will be asked about their pain levels using VAS. Additional medications/treatments, will be given according to its instructions for use. Day 1-Day 84 Follow-Up Period Subjects will return to the site for study visits on Days 2, 4, 7, 14, 21, 28, 56 and 84 for efficacy and safety assessments. For subjects having unresolved AEs on Day 84, an unscheduled visit will be set 6-8 weeks after Day 84 to verify the resolution of the AE. On that visit, follow up of using photographs C-CAT and S-CAT will also be conducted. Subjects will be advised to continue their regular diet and physical activity during the study. Safety assessments include vital signs, ECG, AEs severity assessment, and treatment area evaluation. Treatment area evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures. Specifically, degree of swelling severity will be assessed as a function of time and in each visit Subjects will be asked about their pain levels using VAS. Pain at injection site will not

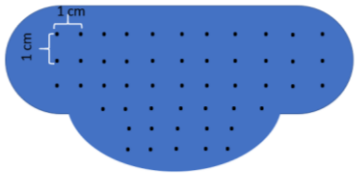
	be recorded as an AE but the information regarding pain will be obtained from the VAS scores completed by the subject. Concomitant medications will be recorded.
Sample Size	Up to 75 subjects (5 in each treatment group in stage 1 of the study and up to 10 subjects in each treatment group in stage 2 of the study).
Study Population	Adult volunteers age 18 to 65 years who have consented to participate in this study.
Main Inclusion Criteria	For a subject to be eligible for this study, he or she must meet **all** of the following criteria: 1. Is a male or female subject between the ages of 18 and 65 years, inclusive. 2. Has body mass index (BMI) between >22 kg/m^2 and <40 kg/m^2. 3. Has SMF bulge that is contiguous and fits to 32±4 injections sites according to a grid with 1 centimeter (cm) distance between injection points. 4. Has grade 3 to 4 of SMF as rated by both the C-CAT and S-CAT. 5. Has stable weight, with no fluctuation of >5 kg in the past 12 months. 6. If female, is not pregnant or breastfeeding based on the following: a. agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 4 weeks after the last day of study drug and a negative serum pregnancy test (ß-hCG) at screening and negative urine pregnancy test at baseline; or b. is abstaining c. is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy); or d. is confirmed postmenopausal status (defined as either having amenorrhea for ≥ 12 consecutive months without another cause or documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL or another documented medical condition (e.g., was born without a uterus)) NOTE: The following are considered highly effective contraceptive methods: hormonal oral contraceptives, injectables, and patches; intrauterine devices; double-barrier methods (synthetic condom, diaphragm, or cervical cap used with spermicidal foam, cream, or gel); and male partner sterilization. 7. If male (with or without vasectomy), agree to the use of highly effective contraceptive methods as listed above in criteria 7 as well as to use a barrier method, e.g. condom , from study check-in until 7 days after drug injection. 8. Is willing to avoid strenuous exercise for seven (7) days post treatment. 9. Is able to adhere to the visit schedule and protocol requirements and be available to complete the study. 10. Is willing and able to sign an Institutional Review Board (IRB) approved informed consent form (ICF) indicating that they are aware of the investigational nature of the study.
Main Exclusion Criteria	Subjects must **NOT** meet any of the following Exclusion criteria to be eligible for enrollment: 1. Is unable to tolerate subcutaneous injections. 2. Has any systemic disease including but not limited to gastritis or ulcers, renal dysfunction, hypertension, liver disease, glaucoma, diabetes and/or cardiovascular disease, , regardless of whether the condition is controlled with medication. 3. Has any contraindications to oral corticosteroids (methylprednisolon), NSAIDs (e.g., Celecoxib) or non-sedative antihistamines (e.g. cetirizine)

	4. Has skin laxity (i.e., elastosis, skin crepiness, skin redundancy, skin draping, vertical and/or horizontal skin bands and folds, blunting of cervical mental angle, loss of opposition of skin to underlying neck structures due to skin laxity) that could obscure the evaluation and treatment of SMF. 5. Has any scars, unshaven hair, tattoos, facial hair or jewelry on or near the proposed treatment area. 6. Has presence of structures or confounding factors that may interfere with assessing SMF such as but not limited to enlarged submandibular salivary and/or parotid glands, micrognanthia, chin implant, soft tissue volume augmentation of chin and/or jawline, pronounced platysmal bands and deep necklace lines or presence of facial jowls that could obscure the evaluation of SMF. 7. Has a fat bulge under the chin that is too large to be adequately treated by 32±4 contiguous injections on a 1cm grid . 8. Has a fat bulge under the chin that is of an insufficient volume to allow 32±4 injections within a contiguous 1 cm grid. 9. Has significant history or current evidence of a medical, psychological or other disorder that, in the Investigator's opinion, would preclude enrollment in the study. 10. Has an active bacterial, fungal, or viral infection in the proposed treatment area. 11. Has a pre-existing skin condition in the submental region that, at the Investigator's discretion, may confound evaluation or analysis. 12. Has previously had treatments or surgery in the submentum, such as but not limited to, focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate, or neck lift. 13. Has pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia, or facial nerve palsy. 14. Has Dercum's Disease. 15. Has allergic reactions to injectables 16. Has allergic reactions to cetirizine or Celecoxib. 17. Has any pre-existing medical condition other than increased SMF that, at the Investigator's discretion, may result in increased submental fullness, such as but not limited to, thyroid enlargement, goiter, cervical lymphadenopathy, etc. 18. Has a planned fat reduction procedure of any variety to the submental region for the duration of the study. 19. Has medication or a history of coagulopathy. 20. Has a history or family history of venous thrombotic disease. 21. Has been treated chronically at least three (3) months prior to study entry with systemic steroids or immunosuppressive drugs. 22. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs) 23. Has used anticoagulation therapies that may increase bleeding or bruising (i.e., aspirin, ibuprofen/Celecoxib, warfarin, vitamins, and herbal preparations) for seven (7) days prior to treatment. 24. Has had treatment with botulinum toxin injections in the neck or chin area within nine (9) months prior to screening. 25. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study. 26. Claustrophobia or MRI incompatible device or implant.
Dosage and Administration of Study Drug	Subjects will receive study treatments in accordance with the treatment group to which the subject is randomized: | | **Group 1** | **Group 2** | **Group 3** | **Group 4** | **Group 5** | | Day 1 | RZL-012 | RZL-012 + 1% lidocaine with | RZL-012 + methylpredn | RZL-012 + | RZL-012 + |

		1:100,000 epinephrine (10 minutes prior to RZL-012)	isolone dose pack (the first dose of 2 tablets (8mg) is administered 1-2 hours prior to RZL-012) A total of 24 mg (16 mg after RZL-012, as per IFUs)	200 mg Celecoxib BID and 10 mg cetirizine BID (the 1st dose is administered 1-2 hours prior to RZL-012).	pressure garment
Day 2			20 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 3			16 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 4			12 mg methylprednisolone	200 mg Celecoxib BID and 10 mg Zyrtec BID	pressure garment
Day 5			8 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 6			4 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment

BID = twice daily,

RZL-012 will be administered via multiple injections (32±4) for a total dose of 240±30 mg. Each injection point will be dosed with 7.5 mg RZL-012 in a volume of 0.15 mL/injection site. The total injection volume for all groups will be 4.8 mL±0.6.

	Subjects will be injected with RZL-012 perpendicularly (90°) to the skin. An ice pack will be placed on the injected area for pain relief immediately after injection. Subjects will remain seated in the injection position for an additional 10 minutes after dosing. The injection pattern will be based on a submental area shaped grid in which the distance between rows and columns will be 1 cm, as seen in the figure below. The Investigator will choose 32±4 sequential points on the grid that will mark the injected area according to SMF fullness and convexity. The treatment area boundary: superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone. 
Safety Analysis	AEs will be collected and reviewed to evaluate the safety and tolerability of RZL-012. AE collection will begin after dosing and will end at on Day 84. For subjects having unresolved AEs on Day 84, an unscheduled visit will be set 6-8 weeks after Day 84 to verify the resolution of the AE. Other safety measures will include vital sign measurements, laboratory parameters, ECG, and treatment area evaluation including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, , pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures. Specifically, swelling severity will be assessed in each visit, subjects will be asked about their pain levels. Pain at injection site will not be recorded as an AE but the information regarding pain will be obtained from the VAS scores completed by the subject. AEs related to nerve injury will be AEs of special interest. Concomitant medications will be recorded.
Statistical Analysis	All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency, and 95% confidence interval (CI) for proportions by study arm. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variations (CV%), median, minimum and maximum, and 95% CI for means of variables by study arm. **Primary endpoint and exploratory endpoints will be analyzed in descriptive manner.** The data will be analyzed using the SAS version 9.4 (SAS Institute, Cary North Carolina).
Study Duration	It is planned that each subject will participate in the study for 4 months, which comprises a screening period, baseline/treatment period, and follow up period.
Study Centers	6 clinical centers

1.2 Schedule of Activities

Study Procedure	Screening	Baseline (Treatment)	Post Baseline Visit Schedule							
Study Day	**Day (-28) through Day (-1)**	**Day 1**	**Day 2**	**Day 4**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56**	**Day 84**
Signed informed consent	X									
Medical history	X									
Physical Exam	X				X					X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Pregnancy ß-hCG	X									
Pregnancy urine test (women)		X								X
Weight measurements	X	X						X		X
Height measurement	X									
Biochemistry Lab parameters	X		X		X			X		X
ECG	X				X					X
Vital signs	X	Pre X post	X	X	X	X	X	X	X	X
Randomization	X									
Injection of RZL-012		X								
Clinician Chin Assessment Tool (C-CAT)	X	X						X	X	X
Subject- Self-Chin Assessment Tool (S-CAT)	X	X						X	X	X
Subject's Satisfaction questionnaire for SMF appearance	X							X	X	X
2D Standardized photography	X		X	X	X	X	X	X	X	X
MRI	X									X
AEs including VAS		X	X	X	X	X	X	X	X	X

2.0 INTRODUCTION

1.1. Study Rationale

The recent clinical study (RZL-012-SMF-P2b-US-001) was a double-blind, randomized, three-arm, placebo-controlled Phase 2b study that tested the efficacy and safety of RZL-012 injections into the submental fat in 151 subjects. Single administration of high dose RZL-012 (50mg/ml) resulted in a clinically meaningful reduction in submental fat. The efficacy of the RZL-012 high dose was higher than that of the low dose and of the placebo. Local injection-site reactions were the most commonly reported AEs with injection-site pain, nodules induration and edema being clearly RZL-012 related. Injection-site severe swelling in the submental area was shown to be associated with additional AEs such as dysphagia, dysphonia, and dyspnea.

This clinical trial will assess ways to reduce AEs related to swelling and pain.

1.2. Scientific Background

RZL-012 is a cytolytic drug - it disrupts cell membrane integrity which results in necrotic cell death. RZL-012 demonstrated a cell killing effect on cultured adipocyte, fibroblasts and HepG2 cells with IC_{50} values ranging between 20-100 μM. In vivo pig studies demonstrated liponecrosis at the injection site, followed by a transient inflammatory response and finally, a healing process in which fibrotic tissue replaces previous fat tissue. Necrosis of fat tissue at the injection site was seen as early as 24 hours after injection and was still evident 2 weeks later but completely cleared by 12 weeks post dosing. A macrophage-mediated inflammatory response was also prominent at 24 hours and 14 days after injection with only minimal signs of inflammation remaining by 12 weeks post dosing. Fibrosis showed a different pattern compared with liponecrosis and inflammation, starting at 14 days post dosing and becoming much more prominent at 12 weeks post dosing. In essence, RZL-012 enabled de-novo generation of fibrotic tissue to replace excess fat tissue at selected anatomical sites.

To date, Raziel has conducted several clinical studies under INDs to evaluate the safety and efficacy of RZL-012 for local fat reductions, including obesity (INDs 119941, 133324), lipomas of Dercum's Disease patients and SMF (IND 135762) and SMF and flank reduction (IND 154260). Across all clinical trials approximately 222 subjects have received single doses of RZL-012 ranging from 5 mg to 412 mg per subject.

1.2.1. Non-Clinical Studies

The mechanism of action of RZL-012 has been studied in in-vitro studies and in in-vivo studies in pigs (domestic Yorkshire crossbred swine). Pigs were chosen for these studies because their subcutaneous fat resembles that of humans. RZL-012 injected into SC pig fat first caused liponecrosis at the injection site, followed by a transient inflammatory response and finally by a healing process in which fibrotic tissue replaced previous fat tissue.

Safety pharmacology studies of RZL-012 in male Sprague Dawley rats demonstrated that RZL-012 has no effects on the central nervous system functions, or on the respiratory system, on ECG parameters or blood pressure. Safety pharmacology studies of RZL-012 in domestic Yorkshire crossbred swine demonstrated no effects on ECG parameters or blood pressure.

Single and chronic toxicology studies were conducted in Sprague-Dawley rats and in pigs. Local, dose-related skin reactions included fibrosis, inflammation, degeneration/necrosis, atrophy and epidermal hyperplasia. Systemic reactions included increased blood urea nitrogen [BUN], increased creatinine and aspartate aminotransferase [AST] levels and histopathological changes in kidneys (necrosis in tubular epithelium).

Rat embryo-fetal development (EFD) and fertility and early embryo-fetal development (FEED; fertility) studies demonstrated no changes on fertility and reproduction in males and females.

Further details on mechanism of action, safety pharmacology, and toxicology of RZL-012 are provided in the investigator's brochure (IB).

1.2.2. Clinical Studies

To date, approximately 222 subjects have received single doses of RZL-012 ranging from 5 mg to 412 mg per subject across 8 clinical trials (Table 1).

Table 1 Estimated Cumulative Exposure from Clinical Studies

Study Number	Study Population	RZL-012		Placebo
		N	Dose (mg)	N
RZL-012-P0-US-001	Healthy Subjects (Phase 0 obesity)	18	5-20	6
RZL-012-P2a-US-001	Healthy subjects (Phase 2a obesity)	24	40-180	7
RZL-012-FD-P2a-US-001	Lipedema (Phase 2a)	6	60-80	0
RZL-012-FD-P2a-US-001	DD (Phase 2a)	6	30-40	0
RZL-012-DD-P2b-US-001	DD (Phase2b)	29	40-240	18
RZL-012-SMF-P2a-US-001	Submental Fat (Phase 2a)	18	70-210	10
RZL-012-hADMEC14-001	Human ADME study	6	72.9	0
RZL-012-SMF-P2b-US-001	Submental Fat (Phase 2b)	103	142-270	48
RZL-012-FL-P2US-001	Subjects with Flank Fat	12	412	0
	Overall Total Number of Subjects	**222**	**-**	**89**

All clinical trials were conducted in the US, and in all trials RZL-012 was administered via multiple injections during a single injection session.

1.2.2.1. Clinical Trials in SMF

Three clinical trials have been conducted to assess the efficacy and safety of RZL-012 in reducing fat in the submental area. One trial (study RZL-012-SMF-P2a-US-001) was a single-blind, randomized, placebo-controlled, phase 2a, 2-cohort study. The second trial (study RZL-012-SMF-P2b-US-001) was a double-blind, randomized, three-arm, placebo-controlled Phase 2b study. Both studies were completed. The third trial (Study RZL-012-SMFC-P2-US-001) is An Open-Label Phase 2 Study to Compare the Pharmacokinetics, Efficacy and Safety of

RZL-012 in Chinese Subjects Seeking Submental Fat Reduction vs. Non-Chinese Subjects Seeking Submental Fat Reduction. Study enrollment has been initiated recently.

Study RZL-012-SMF-P2a-US-001

Study RZL-012-SMF-P2a-US-001.2 was a single-blind study conducted in 28 subjects with submental fat. An assessment of efficacy was based on the Physician global assessment scale, SMF volume change (MRI), and subject's Face-Q satisfaction questionnaire.

All subjects received a single dosing session and were followed up for 84 days. RZL-012 low dose (N=8) received an average injected dose of 80 mg/subject, RZL-012 high dose (N=10) an average injected dose of 158.5 mg/subject. Ten subjects received placebo. Based on a physician global assessment scale (physicians were not blinded to study treatment), 17/18 of RZL-012 treated subjects demonstrated an improvement in submental fat appearance on 84 days after treatment vs. baseline. None of the placebo subjects demonstrated any change in submental fat appearance on Day 84 vs. baseline. According to the Subject Face-Q Questionnaire (subjects were blinded to study treatment), subjects reported satisfaction regarding perceived effects of RZL-012 on submental fat appearance. The RZL-012 low dose group had a 2.4-fold increase in mean subject satisfaction score, the RZL-012 high dose group showed a 2.5-fold increase in mean subject satisfaction score while the placebo group did not demonstrate an improvement in satisfaction on Day 84 vs. baseline. These Clinician Reported Outcome (CRO) and Patient Reported Outcome (PRO) were correlated with the objective measure of MRI, determined on Day 84 vs. baseline. The high dose RZL-012 group showed a volume reduction of -22.2% ± 14.9 ($p<0.05$ vs the placebo group), the low dose RZL-012 group showed a volume reduction of -10.6% ± 14.5 ($p=0.67$ vs the placebo group, NS) and the placebo group demonstrated a volume reduction of -0.4% ± 13.9.

Study RZL-012-SMF-P2b-US-001

Study RZL-012-SMF-P2b-US-001 was a double-blind, randomized, three-arm, placebo-controlled Phase 2b study conducted in 151 subjects with submental fat. Forty-eight subjects were randomized to the placebo group, 53 subjects to the RZL-012 low dose (183.6 mg) group and 50 subjects to the RZL-012 high dose (270 mg) group. An assessment of efficacy was based on the Clinician Assessment Tool (C-CAT), Subject Self-Chin Assessment Tool (S-CAT); and SMF volume via MRI and caliper-measured submental thickness. Raziel met the primary and secondary endpoints of the study. The proportion of subjects that had an improvement of at least 1 grade using the C-CAT and proportion of subjects who had an improvement of at least 2 grades in both C-CAT and S-CAT in the same subject were statistically significantly higher in RZL-012 high dose vs. placebo. The MRI results demonstrated a volume reduction of -14.9%, -8.3% and no reduction in volume in RZL-012 high dose, low dose and placebo, respectively. Results were statistically significant.

1.3. Risk-Benefit Assessment

1.3.1. Identified RZL-012 Risks

Adverse Events

Identified risks are local injection-site reactions including injection-site bruising, induration, edema, pain, and erythema which are commonly reported after injection of RZL-012. Most

injection site reactions are transient and are not observed for more than 28-56 days following injection. None of these identified risks are serious in nature.

Submental swelling and dysphagia have also been identified as common risks. These two are transient and have not been serious in nature.

In addition, nerve damage was also reported in association with RZL-012 treatment. While these AEs should be carefully monitored, it is noted that there were no serious outcomes to any of these events and all were short-lived.

Laboratory - D-Dimer

Treatment with RZL-012 causes a transient increase in D-dimer without any clinically significant activation of the coagulation system nor any presence of Disseminated Intravascular Coagulation (DIC). The absence of any clinical symptoms related to elevation of D-dimer supports a direct link between RZL-012 induced inflammation and elevated D-dimer levels, unrelated to venous thromboembolic disease.

Laboratory – ALT and AST

RZL-012 is associated with a transient increase in AST which is seen as early as one day following RZL-012 treatment and has resolved by 7 days post-treatment. It is noted that the increase has not been associated with any increases in other liver enzymes, nor with any clinical symptoms, other than in one subject in study RZL-012-P0US-01.3, who received a small single dose of 20 mg of RZL-012. This subject demonstrated a significant transient increase in alanine aminotransferase (ALT) blood levels (Levels had x7-9-fold increase from the upper limit of normal (ULN) on Days 14 and 21, respectively) and a moderate elevation of aspartate aminotransferase (AST) blood levels (~4 fold increase from ULN) 14 days following injection of the highest dose of active treatment (20 mg/subject). Resolution for AST elevated levels and reduction for ALT levels to Grade 1 (mild), occurred 14 days following detection (i.e. 28 days after dosing). ALT levels were normal on the next visit on Day 56. Other liver enzymes such as GGT and alkaline phosphatase, as well as bilirubin levels remained within normal range.

The relationship between RZL-012 injection and a potential increase in liver enzymes is not completely understood. In preclinical studies which were conducted by Raziel, a rise in AST enzyme levels was observed in the high doses female rat group (20 mg/rat (about 80 mg/kg), equivalent to a human dose >900 mg/subject), returning to normal levels within 14 days of recovery. Raziel Therapeutics continues to monitor closely for any changes in liver enzymes.

1.3.2. Benefits

The cytolytic effect of RZL-012 has been demonstrated in non-clinical in-vitro and in-vivo studies. When administered into subcutaneous tissue, this cytolytic effect translates into a reduction in subcutaneous tissue. The reduction in submental fat has been demonstrated in Phase 2a and Phase 2b studies. Confirmatory Phase 3 studies will be conducted.

3.0 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- The primary objective of this study is to compare the benefits of lidocaine, methylprednisolone, Celecoxib + cetirizine or compression garments on RZL-012-induced adverse events.

3.1.2 Secondary Objectives

- To assess the safety profile of RZL-012 of combining lidocaine, methylprednisolone , Celecoxib + cetirizine or compression garment with RZL-012

3.2 Study Endpoints

3.2.1 Primary Endpoint

- Safety profile of combining lidocaine, methylprednisolone , Celecoxib +cetirizine or a compression garment with RZL-012.

3.2.2 Exploratory Endpoints

The secondary endpoints for the study are:

- Proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications.
- Proportion of subjects who have at least a 1-grade improvement in the S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications.
- Proportion of subjects who have at least a 1-grade improvement in both C-CAT and S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications.
- Proportion of subjects who have at least a 2-grade improvement in both C-CAT and S-CAT on Day 84 versus baseline in subjects receiving RZL-012 alone or in combination with other medications.
- Changes in SMF volume measured by MRI scans on Day 84 versus baseline in subjects

receiving RZL-012 alone or in combination with other medications.

- Satisfaction in subjects receiving RZL-012 alone or in combination with other medications.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2, open-label, 2-stage, adaptive-design study in which subjects will be randomized into one of 5 treatment groups comprised of RZL-012 with or without additional study treatments:

1. RZL-012 alone

2. RZL-012 and 1% lidocaine with 1:100,000 epinephrine (on Day 1) – 5ml lidocaine will be injected 10 minutes before RZL-012 treatment.

3. RZL-012 and oral methylprednisolone dose pack (8 mg (2 tablets) on Day 1 before treatment followed by 16 mg after treatment (as per Instructions for Use)). From Day 2, a daily tapering off by 4 mg until Day 6 will be administered per Rx Instructions for use.

4. RZL-012 and Celecoxib and cetirizine (200 mg Celecoxib BID and 10 mg cetirizine BID on Days 1, 2, 3, 4, 5 and 6).

5. RZL-012 + sling/pressure garment (until Day 6).

In the first stage of the study, 5 subjects will be randomized into each of the treatment groups. Study outcomes will be assessed up to one week thereafter to determine the need to modify additional study treatments. Subsequently up to 10 additional subjects will be randomized into each of the treatment groups for the second stage of the study.

For each subject, the study will consist of a screening period, baseline period in which subjects will receive a single treatment session of RZL-012 with the assigned treatment and a follow-up period. RZL-012 will be administered during a single treatment session via multiple injections into the submental area under the chin. Subjects will thereafter be monitored for safety and efficacy for at least 84 days.

Each subject will be treated with the same dose of RZL-012 :

- RZL-012 (concentration of injected solution 50 mg/mL RZL-012) of 7.5 mg/0.15 mL/injection point that results in a total dose/volume of 240±30mg mg/4.8±0.6 mL RZL-012,

Each subject will receive additional study treatments in accordance with the treatment group to which the subject is randomized.

4.2 Rationale for Study Design

Because there are 5 different treatment arms, and subjects receive different additional study treatments depending on the treatment arm to which the subject is randomized, blinding of study treatments would be difficult. Therefore, the study will employ an open-label design.

4.3 Rationale for Study Dose

The Phase 2b study (RZL-012-SMF-P2b-US-001) demonstrated that a single treatment session of RZL-012 at a maximal dose of 270 mg into the subcutaneous tissue of the submental area reduces fat and improves appearance of this area. Therefore, Raziel intends to proceed with this dose into Phase 3 clinical trials.

5.0 STUDY POPULATION

5.1 Inclusion Criteria

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

1. Is a male or female subject between the ages of 18 and 65 years, inclusive.
2. Has body mass index (BMI) between >22 kg/m2 and <40 kg/m2.
3. Has SMF bulge that is contiguous and fits to 32±4 injections sites according to a grid with 1 centimeter (cm) distance between injection points.
4. Has grade 3 to 4 of SMF as rated by both the C-CAT and S-CAT.
5. Has stable weight, with no fluctuation of >5 kg in the past 12 months.
6. If female, is not pregnant or breastfeeding based on the following:

   agree to the use of highly effective contraceptive methods for at least 2 weeks before baseline until 4 weeks after the last day of study drug and a negative serum pregnancy test (ß-hCG) at screening and negative urine pregnancy test at baseline; or

   is abstaining

   is of nonchildbearing potential defined as clinically infertile as the result of surgical sterilization (hysterectomy, bilateral tubal ligation, and/or bilateral oophorectomy); or

   is confirmed postmenopausal status (defined as either having amenorrhea for ⩾ 12 consecutive months without another cause or documented serum follicle-stimulating hormone (FSH) level > 40 mIU/mL or another documented medical condition (e.g., was born without a uterus))

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

5.2 Exclusion Criteria

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

1. Is unable to tolerate subcutaneous injections
2. Has any systemic disease including but not limited to gastritis or ulcers, renal dysfunction, hypertension, liver disease, glaucoma, diabetes and/or cardiovascular disease, regardless of whether the condition is controlled with medication.
3. Has any contraindications to oral corticosteroids (prednisone), NSAIDs (e.g., Celecoxib) or non-sedative antihistamines (e.g. cetirizine)
4. Has skin laxity (i.e., elastosis, skin crepiness, skin redundancy, skin draping, vertical and/or horizontal skin bands and folds, blunting of cervical mental angle, loss of opposition of skin to underlying neck structures due to skin laxity) that could obscure the evaluation and treatment of SMF.
5. Has any scars, unshaven hair, tattoos, facial hair or jewelry on or near the proposed treatment area.
6. Has presence of structures or confounding factors that may interfere with assessing SMF such as but not limited to enlarged submandibular salivary and/or parotid glands, micrognanthia, chin implant, soft tissue volume augmentation of chin and/or jawline, pronounced platysmal bands and deep necklace lines or presence of facial jowls that could obscure the evaluation of SMF.
7. Has a fat bulge under the chin that is too large to be adequately treated by 32±4 contiguous injections on a 1cm grid .
8. Has a fat bulge under the chin that is of an insufficient volume to allow 32±4 injections within a contiguous 1 cm grid.
9. Has significant history or current evidence of a medical, psychological or other disorder that, in the Investigator's opinion, would preclude enrollment in the study.
10. Has an active bacterial, fungal, or viral infection in the proposed treatment area.
11. Has a pre-existing skin condition in the submental region that, at the Investigator's discretion, may confound evaluation or analysis.
12. Has previously had treatments or surgery in the submentum, such as but not limited to, focused ultrasound, radiofrequency, cryolipolysis, liposuction, sodium deoxycholate, or neck lift.
13. Has pre-existing neurological or gastrointestinal condition leading to dysphagia, dysphonia, or facial nerve palsy.
14. Has Dercum's Disease.
15. Has allergic reactions to injectables
16. Has allergic reactions to cetirizine or Celecoxib.
17. Has any pre-existing medical condition other than increased SMF that, at the Investigator's discretion, may result in increased submental fullness, such as but not limited to, thyroid enlargement, goiter, cervical lymphadenopathy, etc.

18. Has a planned fat reduction procedure of any variety to the submental region for the duration of the study.
19. Has medication or a history of coagulopathy.
20. Has a history or family history of venous thrombotic disease.
21. Has been treated chronically at least three (3) months prior to study entry with systemic steroids or immunosuppressive drugs.
22. Has been treated chronically at least one (1) week prior to study entry with non-steroidal anti-inflammatory drugs (NSAIDs)
23. Has used anticoagulation therapies that may increase bleeding or bruising (i.e., aspirin, ibuprofen/Celecoxib, warfarin, vitamins, and herbal preparations) for seven (7) days prior to treatment.
24. Has had treatment with botulinum toxin injections in the neck or chin area within nine (9) months prior to screening.
25. Current participation or participation within three (3) months prior to the start of this study in a drug or other investigational research study.
26. Claustrophobia or MRI incompatible device or implant.

6.0 STUDY INTERVENTION

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

RZL-012 is provided as a sterile liquid solution suitable for injection. It has a concentration of 50 mg/mL. It is packaged in glass vials and supplied in study kits.

Subjects will be treated with additional planned treatments in accordance to their randomization group. In case subjects will be assigned to group 2, they will be injected with 5 mL lidocaine with 1:100,000 epinephrine. In case subjects will be randomized to group 3 or 4 they will receive a prescription to buy in the pharmacy the relevant drugs, i.e. methylprednisolone dose pack (if assigned to group 3) and Celecoxib and cetirizine (in case assigned to group 4). This is in order to allow them to take the drugs at baseline visit (Day 1) prior to RZL-012 injection. Subjects will take medicines 1-2 hours prior to RZL-012 injection and continue after RZL-012 injection per instructions for use for each of the medicines for a total period of 6 days. If subjects are randomized to group 5, they will be given with the pressure garment in the site immediately after injection and will wear the garment up to day 6 after injected. Description of group assignments is described in Table 2.

Table 2– Study Group Treatment

	Group 1	Group 2	Group 3	Group 4	Group 5
Day 1	RZL-012	RZL-012 + 1% lidocaine with 1:100,000 epinephrine (10 minutes prior to RZL-012)	RZL-012 + methylprednisolone dose pack (the first dose of 2 tablets (8mg) is administered1-2 hours prior to RZL-012) A total of 24 mg (16 mg after RZL-012, as per IFUs)	RZL-012 + 200 mg Celecoxib BID and 10 mg cetirizine BID (the 1st dose is administered 1-2 hours prior to RZL-012).	RZL-012 + pressure garment
Day 2			20 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 3			16 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 4			12 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 5			8 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment
Day 6			4 mg methylprednisolone	200 mg Celecoxib BID and 10 mg cetirizine BID	pressure garment

BID = twice daily,

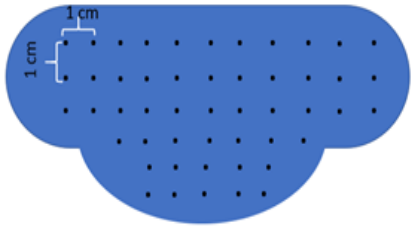
Subjects will undergo a single treatment session with maximum 36 injections of 7.5 mg RZL-012 each for a total RZL-012 dose of 270 mg. The total injection volume for all groups will be 4.8 mL±0.6.

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

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

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

Figure 1 Submental Injection Pattern



6.2 Preparation/Handling/Storage/Accountability

The RZL-012 solution is supplied ready to use. The RZL-012 kits, each comprised of 2 vials, should be stored in the site pharmacy or clinic at monitored room temperature conditions (22 ± 7 °C) and protected from light. They should be kept in a secure location physically separated from standard clinic or office drug supplies.

RZL-012 is administered to the subject on the study site by the study investigator. The vials should be manually shaken prior to injection.

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

1. The lower face and anterior neck will be cleaned with an appropriate topical antiseptic.
2. Ice/cold pack or topical local anesthesia (i.e., lidocaine cream) may be used prior to drug administration to enhance subject's comfort.
3. The treatment area will be bounded superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone.
4. Injection grid pattern will be applied by pressing the grid firmly onto the clean, dry skin, with the printed grid pattern facing the skin. The grid paper backing will be thoroughly wetted with a cotton pad soaked with sterile water. After 15 seconds, the grid cover will be peeled off.
5. An area of 32±4 adjacent injection points will be determined following the Investigator's evaluation.
6. Syringes will be filled with 1 mL RZL-012 and the number of syringes will be compatible with the total volume of injection. Up to six (6) syringes for a total volume of 5.4 mL will be used.

7. All injections will be administered perpendicularly in 90 degrees, using a 1 mL Luer-lock syringe and a 29G or 27G x 1/2" needle, respectively.

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

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

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

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

The number of injections for each subject will be determined by the Investigator according to fullness of SMF but will not be lower than 28 injections or higher than 36 injections. Total injection volume and number of injection per subject should be recorded on medical records.

All study drug received by the Investigator will be inventoried and accounted for in a Dispensing Log.

A maximal of 2 vials will be used for each subject. All open vials will be kept until the end of study when the Sponsor will determine if study drug should be returned or destroyed.

6.3 Study Intervention Compliance

Study treatment consists of a single administration session administered by the study investigator.

6.4 Prior and Concomitant Medications

Concomitant medications are defined as medications taken any time after the start of dosing until discharge assessments. All concomitant medication, including blood and blood products, dietary supplements, and non-prescription drugs, will be listed at screening/baseline. Each entry will include the treatment's start date, treatment name (generic), reason for use, dosing regimen (dose and frequency of use), route of administration, and stop date (if applicable). 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.

7.0 STUDY INTERVENTION DISCONTINUATION

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the protocol. Subjects can be prematurely discontinued from the study for one of the following reasons:

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

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

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 Medical History

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

8.2 Height

Height will be measured at screening. It will be reported in centimeters. A subject's height together with weight will be used to calculate a subject's BMI.

8.3 Weight

Body weight will be measured at screening, baseline (day 1) and at the study visit Day 28 and study visit Day 84. Weight will be reported in kilograms (kg). A subject's weight at screening together with height will be used to calculate a subject's BMI.

8.4 Pregnancy Tests

A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening and a urine pregnancy test will be administered at baseline prior to dosing. Additional serum pregnancy tests will be done at any time during the study (up to Day 84), if pregnancy is suspected. Urine pregnancy test will be done to females of childbearing potential on Day 84.

8.5 Complete Physical Examination

The Investigator (or medically qualified nominee) will perform a complete physical examination at screening and on Day 7 and Day 84 visit.

8.6 Clinician-Chin Assessment Tool (C-CAT)

SMF ratings using the C-CAT will be conducted by a fixed and well-trained Investigator at screening and baseline (Day 1) and at study visits on Days 28, 56, and 84 to assess the change in SMF severity before and following treatment.

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

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

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

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

A comprehensive training guide with representative photographic examples and line drawing to each grade will be provided to the study center sites for training and visual comparison.

Table 3 Clinician Chin Assessment Tool (C-CAT)

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

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

SMF ratings using the S-CAT will be conducted by the subject at screening and baseline (Day 1) and at study visits on Days 28, 56, and 84 to assess the change in SMF area following treatment.

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

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

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

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

Table 4 Self Chin Assessment Tool (S-CAT)

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

8.8 Magnetic Resonance Imaging (MRI)

The purpose of the MRI exam is to evaluate whether the additional treatments (i.e., lidocaine, Celecoxid, Zyrtic etc.) affects the fat reduction following treatment of RZL-012. MRI exams will be conducted in imaging centers close to selected clinical sites.

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

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

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

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

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

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

8.9 2-D Standardized Photography

Standardized photography (2-dimensional) of the face (SMF area) will be conducted at screening and on study visits Day 2, Day 4, Day 7, Day 14, Day 21, Day 28, Day 56, and Day 84.

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

8.10 Subject's Satisfaction Questionnaire

Subject's satisfaction questionnaire (yes/no questions) will be conducted by the subjects at screening and on study visits Day 28, Day 56 and Day 84.

Subjects will be asked the following questions and will score their satisfaction based on the grades below:

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

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

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

Score	**Grade**
0	Extremely Satisfied
1	Satisfied

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

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

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

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

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

8.11 Biochemistry

Blood samples for the laboratory evaluation of biochemistry parameters will be collected at screening and at study visits Day 2, Day 7, 28 and Day 84.

If there are clinically significant alerts obtained on Day 7, an unscheduled visit will be added for additional blood sampling.

Complete blood cell count (CBC) will include a standard red blood cell (RBC), white blood cell (WBC) with differential, hemoglobin, hematocrit, platelets. A comprehensive metabolic panel will include serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, calcium, globulin (calculated), phosphorus, chloride, sodium, potassium, blood urea nitrogen (BUN)/creatinine ratio (calculated), creatinine with GFR estimated, total bilirubin, albumin, albumin/globulin ratio (calculated), total protein, amylase, bicarbonate/carbon dioxide (CO_2), uric acid, gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH).

Biochemistry parameters will be collected for safety assessments.

8.12 Vital Signs

Vital signs (systolic and diastolic sitting position blood pressure, pulse rate, respiratory rate, and body oral temperature) will be obtained at screening, baseline (pre and post dose) and at study visits Day 2, Day 4, Day 7, Day 14, Day 21, Day 28, Day 56 and Day 84.

Vital signs will be collected for safety assessments.

8.13 ECG

ECG tests will be performed at screening and at study visits Day 7 and Day 84. ECG will be performed in triplicates.

ECGs will be collected for safety assessments.

8.14 Visual Analog Scale (VAS)

Pain will be assessed as part of the AEs using Visual Analog Scale (VAS). A scale between 0 to 10 will describe the pain level, where 0 represents no pain and 10 score is intolerable pain. A score of 1-3 is categorized as mild, 4-6 is moderate and 7-10 is severe. VAS will be assessed on Day 1 (after injection), Day 2, Day 4, Day 7, Day 14, Day 21, Day 28, Day 56 and Day 84.

8.15 Adverse Events and Serious Adverse Events

8.15.1 Collection of Adverse Events Data

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (e.g., worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case

report forms only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity. In case the AE severity is changed from one severity grade to the another the date of AE start and AE end of the specific AE severity should be recorded.

The reporting period for AEs starts after dosing of study drug and will end at final study visit. If an AE remains unresolved at discharge, the subject will be followed, at the Investigator's discretion, until resolution of the event or until the subject is deemed "lost to follow-up". SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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

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

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

AEs will be graded for severity according to the following definitions:

Table 5 Severity Assessment of Adverse Events

Common Term	**Description**
Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Assisted Daily Living

Common Term	Description
	(ADL).
Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Life-Threatening	Life-threatening consequences; urgent intervention indicated.
Death	Death related to AE

8.15.2 Serious Adverse Events

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

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

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

8.15.3 Reporting Requirements for Serious Adverse Events

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

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

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

Report SAEs by:

Report SAEs by

SAE Hotline: 888-746-7231

SAE Fax Line: 888-746-3293

SAE Email: rho_productsafety@rhoworld.com

Table 6 Contact Information for SAE Reporting

Primary Contact	**Sponsor Contact**
Lead Product Safety Specialist	**Medical Monitor:**
Bonnie Graham, RN, BSN	**Patricia Walker, MD**
Mobile: Mobile:	Mobile: 1-805-705-5853
Email: Email:	Email: dr.patricia.walker@gmail.com

8.15.4 Reporting pregnancy

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

The investigator must notify the sponsor of any pregnancies in accordance with the SAE reporting procedures described in section 8.14.3. Note, while the pregnancy is not considered an AE or an SAE, any pregnancy complication or newborn complication will be reported as an AE or SAE if it meets the criteria. Follow-up information regarding the course of pregnancy, including perinatal and neonatal outcomes and, where applicable, offspring information must be reported on the Pregnancy Outcome eCRF.

8.15.5 Recording of Serious Adverse Events

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

9.0 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

A total of 75 subjects will be included in the study. All subjects will be treated with RZL-012. Each 15 subjects will be randomized into each of the treatment groups.

9.2 Analysis Data Sets

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

9.3 Endpoints Analyses

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

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

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

Primary endpoint and exploratory endpoints will be analyzed in descriptive manner.

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

9.4 Safety

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

AE assessment and treatment area evaluation including, but not limited to evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus. Pain in the injection site will be assessed by Visual Analog Scale (VAS) in each of the visits. Injection site pain will not be recorded as an AE.

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using MedDRA™ and will be presented by body system.

AEs related to nerve damage such as: paralysis, mandibular neuropathy, facial palsy will be AEs with special interest, i.e., the PI will write a detailed narrative on these specific AEs.

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

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

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

10.0 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

10.1 Data Collection and Reporting

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

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

10.2 Study Monitoring

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

All eCRFs will be 100% source verified against corresponding source documentation (e.g., office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

10.3 Audit and Inspection

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

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

10.4 Deviation from Clinical Trial Protocol

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

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

10.5 Retention of Records

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

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

10.6 Data Disclosure and Subject Confidentiality

Subject medical information and video recordings obtained as a result of this study is considered confidential and used only for study evaluation purposes. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

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

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

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

11.0 PROTECTION OF HUMAN SUBJECTS

11.1 Basic Principles

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

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

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

11.2 Institutional Review Board/Ethics Committee

The Investigator or designee agrees to provide the IRB/EC with all appropriate material, including a copy of the ICF. The study will not be initiated until the Investigator obtains written approval of the research plan and the ICF from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56 (Code of Federal Regulations).

11.3 Informed Consent

Prior to initiation of any study procedures, each subject will undergo an Informed Consent process in which the subject voluntarily confirms their willingness to participate in the trial. The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form (ICF). Written informed consent must be provided by the potential study participant prior to initiation of any screening evaluations or other study-related procedures. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

The ICF approved by the IRB/EC will contain a description of the study's purpose, purpose, procedures, inconveniences and potential risks, and anticipated benefits. Prior to participation in the trial, the subject will receive a copy of the signed and dated written ICF. During participation in the trial, the subject will receive a copy of the signed and dated consent form updates and a copy of any amendments to the ICF provided to the subjects.

After written informed consent is obtained, the subject will be assigned a screening number and will undergo the designated screening procedures listed in Section 1.2. The Investigator, sub-investigator or delegate will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 5.0.

11.4 Subject Health Injury and Insurance

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

11.5 Completion of the Study

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

Appendix A: Photographic Standards of the Face Area