RZL-012 Study Protocol

Protocol Number RZL-012-FD-P2aUS-001.7

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.

Principal Investigator:

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Sponsor:

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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
BAT	Brown-like adipose tissue
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CK-MM	Creatine-kinase MM
C_{max}	Maximum observed concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
EF	Efficacy analysis set
FDA	Food and Drug Administration
FFA	Free fatty acids
FIFO	First In First Out
FOB	Functional Observational Battery
GLP	Good Laboratory Practice
GTTP	Gamma-glutamyltransferase
HbSAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose

Abbreviation or Specialist Term	Explanation
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LEFS	Lower Extremity Functional Scale
LPL	Lipoprotein lipase
MRI	Magnetic Resonance Imaging
NOAEL	No observed adverse effect level
NORD	National Organization for Rare Disorders
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin time
PTT	Partial thromboplastin time
QOL	Quality of life
RBC	Red blood cells
SA	Safety analysis set
SAE	Serious adverse event
SAT	Subcutaneous adipose tissue
SFM	Subcutaneous fat mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal half-life
TAG	Triacylglycerols
TG	Triglycerides
TLA	Tumescent Liposuction (Local Anesthesia)
T_{max}	Time of maximum observed sample concentration
UCP1	Uncoupling protein 1
US/USA	United States/United States of America
WAL	Water Assisted Liposuction
WAT	White adipose tissue

Abbreviation or Specialist Term	Explanation
WBC	White blood cells

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).

Karen L. Herbst		10/22/2019
Investigator's name	Investigator's Signature	Date

PROTOCOL SYNOPSIS

Protocol Number	RZL-012-FD-P2aUS-001
Protocol Title	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 women and men with nodular Dercum's disease.
Study Phase	Phase 2a
Study Drug	RZL-012
Study Objectives	Primary objective: Evaluation of the overall safety of RZL-012 following injection into the subcutaneous fat in patients with lipedema. Secondary objective: Evaluation of 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.
Sample Size	12 subjects
Study Design	This is an open label, 2 cohort clinical trial in women with lipedema with substantial fat above the knee or women and men with nodular Dercum's disease. Each cohort will have 6 subjects who will receive RZL-012. • The 1st cohort will be comprised of subjects with Dercum's disease • The 2nd cohort will be comprised of subjects with lipedema with substantial fat above the knee. Within each cohort, dosing of the subjects will progress consecutively from one individual to the other with a minimum of 7-days between subjects to assess safety. This study design will allow the physicians to monitor safety for at least 7 days prior to dosing the next subject. Cohort 2 will be conducted in a dose escalation manner and the decision to proceed to the next dose level will be made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject. The trial will proceed within a cohort provided that no more than one subject experiences intolerable side effects in a cohort, and based on the decision made by the Principal Investigator (PI) and the Medical Monitor.
Study Population	Post-menopausal 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.

Main Inclusion Criteria	Subjects must meet all the following to be eligible for study participation: 1. 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. 2. For Dercum's disease subjects – at least 2 nodules to be injected of at least 2cm diameter, each, as determined by ultrasound 3. For lipedema subjects - Significant subcutaneous fat above the knee as determined by circumference of 50cm 4. Generally considered healthy according to medical history, physical examination, electrocardiogram (ECG) and laboratory evaluation with a special emphasis on metabolic parameters (fasting glucose concentration < 200 mg/dL, normal blood pressure). 5. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study. 6. Subjects must sign an informed consent indicating that they are aware of the investigational nature of the study.
Main Exclusion Criteria	Subjects meeting any of the following criteria will be excluded: 1. Unable to tolerate subcutaneous injection. 2. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator put the subject at significant risk, are not eligible. 3. Positive blood screen for Hepatitis B surface antigen (HbSAg), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV), or positive urine screen for alcohol or drugs of abuse (unless prescribed by a physician). 4. Subjects with a clinical history of primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids are ineligible. 5. As a result of medical review, physical examination, the PI (or medically qualified nominee) considers the subject unfit for the study. 6. Known sensitivity to components of the injection formulation. 7. Prior wound, tattoo or infection in the treated area. 8. Prior invasive treatment such as surgery or injectable drug at the RZL-012 injected area.

Intolerable Side Effect Definition

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

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

Subjects experiencing an intolerable side effect will be withdrawn from the study, but followed until the event resolves or becomes stable; all actions taken are to be fully documented in source documents and Case Report Forms (CRFs). To be considered an intolerable side effect, such an event must be considered to be possibly or probably related to the study drug

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

- Recurring serious or severe ADR clinically evaluated by PI as warranting study termination.
- A decision made by Sponsor and/or Institutional Review Board (IRB)/Ethics Committee (EC) and/or local regulatory agency to terminate the study.

Study Drug Dosage and Administration

The 1st cohort will be comprised of subjects with Dercum's disease: all subjects will be injected with RZL-012. Dosing will be calculated according to the size of the nodule (diameter) as determined by ultrasound: 5mg/cm^2 reaching a maximal dose of 40mg per subject (1/6.25 the No observed adverse effect level [NOAEL] based on Human Equivalent Dose [HED] from Good Laboratory Practice [GLP] toxicology study).

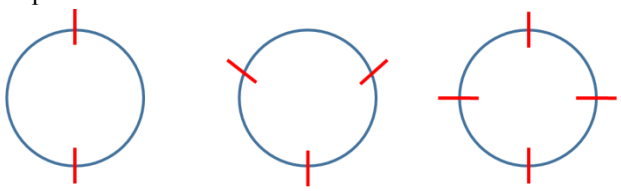
Nodule of 2-2.9cm diameter, as determined by ultrasound, will be injected 2 injections (0.1 mL each, 1 cm apart); total of 10 mg RZL-012.

Nodules of 3-3.9cm diameter, as determined by ultrasound, will be injected 3 injections (0.1 mL each, 1 cm apart); total of 15 mg RZL-012.

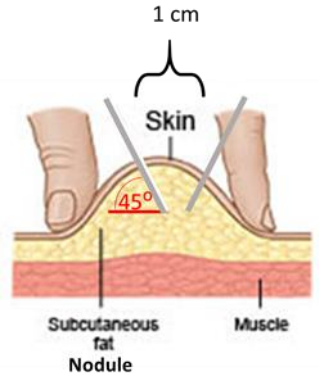
Nodules of 4-8cm diameter, as determined by ultrasound, will be injected 4 injections (0.1 mL each, 1 cm apart); total of 20 mg RZL-012.

Cohort 1			
Number of Subjects – Active	6		
Nodule size – diameter (cm)	2-2.9	3-3.9	4-8
Total Dose of RZL-012 (mg)	10	15	20
Dose per NOAEL*	1/25th	1/18.75th	1/12.5th
Number of Injections	2	3	4

Subjects will receive a single treatment in multiple sites (2-8) of injection according to the design in the picture below:



Injections will be diagonally (45 °) to the skin surface and towards the center of the nodule and the distance between injections in a nodule will be 1 cm (see picture below).



The 2nd cohort will be comprised of subjects with lipedema with substantial fat above the knee.

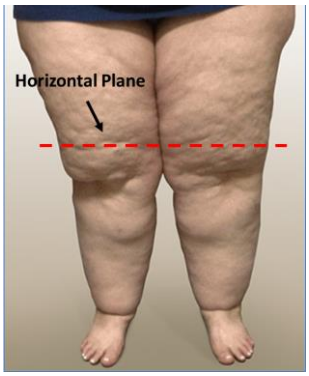
The first 3 subjects will receive 30 mg RZL-012 in 6 injections (0.1mL each) in one leg followed by 30mg RZL-012 (6 injections, 0.1mL each) in the second leg adding up to 12 injections of 60mg RZL-012 (1/4.688th the NOAEL based on HED from GLP toxicology study).

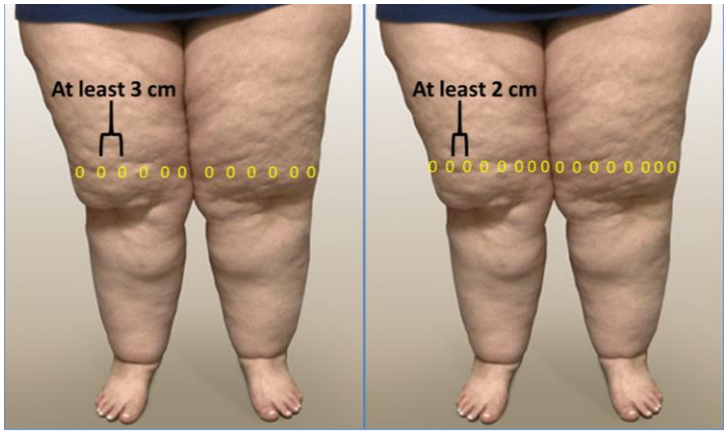
The last 3 subjects will receive 40mg RZL-012 in 8 injections (0.1mL each) in one leg followed by 40mg RZL-012 (8 injections, 0.1mL each) in the second leg adding up to 16 injections of 80mg RZL-012 (1/3.125th the NOAEL based on HED from GLP toxicology study).

Cohort 2		
Number of Subjects – Active	3	3
Total Dose RZL-012 (mg)	60	80
Dose per NOAEL*	1/4.688	1/3.125
Number of Injections	12	16

* based on HED from GLP toxicology study

A grid line will be drawn with a makeup pencil in a horizontal plane (Figure 2) 4-6 cm from the suprapatellar fat and its distance from the floor recorded. An attempt should be made to find palpable nodules along the grid line. The injection sites will be marked in circles with a non-erasable pen. This mark should be intensified upon following visits. Injections will be given in multiple sites (4-8 in each leg), diagonally (45 °) to palpable nodules, in the fat above the knee. An attempt should be made to lift the nodule and inject into the middle of the fat-mass. If no nodules are noted in the horizontal plane, drug will be injected in to the fatty tissue (in this case small nodules seen in ultrasound will be followed for changes). Injections will be on the same horizontal plane.



	Injections will be spread as much as possible and the distance between injected sites will be at least 2-3 cm, according to the number of injections (see picture below).  12 injections of RZL-012 16 injections of RZL-012
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. 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. Subjects may not receive the following medications while on study: • Chronic treatment with systemic steroids or immunosuppressive drugs. • Chronic treatment with Non Steroid Anti-Inflammatory Drugs (NSAIDs) and aspirin. • Any investigational product other than RZL-012. Before dosing, analgesic gels or creams such Lidocaine (e.g., Emla) or Pramoxine should be used to numb the injected site. An ice pack may be applied on the site of injection following dosing to help reduce pain. At day 1 following injection, application of the anti-histamine Benadryl Gel (Diphenhydramine hydrochloride 1 %for topical use only) should be initiated prophylactically, according to drug instructions for use, to avoid itching at the injected area. Benadryl Gel should be applied for 7 days. Use of nattokinase is prohibited and the use of other supplements or complementary medicines/botanicals should be approved by the PI, except for conventional multivitamin supplements. The use of prohibited supplements should be stopped a week before injection.
Study Procedure	Study activities upon study entry will include, but not be limited to: Informed Consent, full medical history, physical examination, vital signs measurements, ECGs, clinical laboratory tests, photography and skin irritancy evaluation of site injection, ultrasound, height and weight measurements, Quality of Life (QOL) and function questionnaire in lipedema subjects, and pain assessment. Periodical site visits will allow assessment of treatment safety and efficacy. Subjects will be advised to keep their regular diet and physical activity.
Visit Schedule (See Table 2)	Subject site visits will be performed ± 1 day from scheduled date for study visits Day 0-28 and 2± 1 days from schedule date for follow-up visits (Day 56). All data relevant for the visit needs to be obtained within 3 days (e.g., blood tests results) of visit. **Screening Day visit (Day -14 through -2):** - Following signing the informed consent - assessment of subject eligibility will include: medical history, physical examination, vital signs, ECG, serology assays (HBV, HCV and HIV), clinical laboratory tests, drug screen. Clinical laboratory tests will include:

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

- In addition, photography and evaluation of skin irritancy by Draize score of the injection site area.
- For Dercum's disease subjects – ultrasound assessing nodules size (diameter) and quality. Determining which nodules are to be injected with a total of 40mg RZL-012.
- For lipedema subjects – measurement of leg circumference above the knee and assessing fat thickness and nodular quality by ultrasound.
- For lipedema subjects - QOL and function questionnaires.

Baseline visit (Day 0):

- Pre-treatment: eligibility confirmation, vital signs, Draize score, leg circumference, clinical evaluation of local pain and tenderness to pressure and nodules size and/or numbers, blood sample for serum chemistry, and hematology baseline level will be taken.
- Treatment - All injections will be administered 45 ° to the skin surface using a 1 mL Luer-lock syringe and a 30 G x 1/2" needle (the hole of the needle pointing into the fat layer).
- Post treatment: ECG (4h and 8h ± 30min post injection), pulse rate (1h, 2h, 4h, 8h, 24h post injection in the opposite hand of blood sampling), vital signs (2h ± 30 min post injection), Draize score (2h post injection ± 30 min), adverse events (AEs) will be recorded.

Schedule visits (Day 1-28):

- Day 1 following treatment will include: ECG, vital signs including pulse rate, Draize score, and photographs of the treated area, clinical evaluation of local pain and tenderness to pressure. Subjects will start applying an anti-histamine gel.
- For safety reasons 24hr ± 2hr following injection, Blood samples for serum chemistry and hematology will be taken
- Day 3 following treatment will include Serum chemistry and hematology.
- Visits will take place every 7 days ± 1d from treatment till Day 28. During visits, all tests (physical exam, vital signs, ECG, clinical laboratory tests, urinalysis, Draize score, leg circumference above the knee, weight measurement, QOL and function questionnaires in lipedema subjects, clinical evaluation of local pain and tenderness to pressure and reduction in nodules size and/or numbers, photographs and ultrasound will be performed according to schedule (Table 2).
- Subjects will be questioned for AEs every visit.
- Subjects will record their daily use of analgesics. Diaries will be checked and data will be captured in the CRFs.

Follow-up visit (Day 56):

- Subjects will be followed on Day 56 following injection.
- A week before Day 56 visit, subjects will record their daily use of analgesics. Diaries will be checked and data will be captured in the CRFs.
- Evaluation of the injected area will be performed by Draize score, photographs, QOL and function questionnaires in lipedema subjects, clinical evaluation of local pain and tenderness to pressure and reduction in nodules size and/or numbers.

	- For Dercum's disease subjects – ultrasound assessing nodules size (diameter) and quality. - For lipedema subjects – measurement of leg circumference above the knee and assessing fat thickness and nodular quality by ultrasound. - Subjects will be questioned for AEs.
Safety Analysis	Safety data from the study will be summarized descriptively by treatment and cohort. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. The nature, frequency, seriousness, severity and relation to study drug of AEs will be tabulated for all subjects combined and by treatment. Change-from-baseline values for vital signs, clinical laboratory and ECG will be summarized. Shift tables of normal / abnormal versus baseline may be presented as well. Draize scores will be presented in tabular format by visit, treatment, and cohort. Serious adverse events (SAEs) will be described in narratives as part of the study report.
Study Endpoints	**Primary Endpoint**: Evaluation of the overall safety of RZL-012 injection into the subcutaneous fat in Derdum's disease and lipedema. The primary safety endpoint is the incidence of intolerable side effects. **Secondary Endpoints**: 1. For lipedema subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline based on ultrasound (reduction in nodules size and/or numbers) and leg circumference above the knee assessments. 2. For Dercum's disease subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline based on ultrasound (reduction in nodules size and/or numbers). 3. Extended duration of the fat reduction effect. To that end, ultrasound images and above the knee circumference measurement will be followed for 56 days. 4. Elucidation of the tissue changes by ultrasound of the injection site to include reduction in fat thickness and nodular quality. 5. Improvement in local pain as measured by Comparative Pain Scale and by the reduction in the use of analgesics. 6. Improvement in QOL and function in lipedema subjects as measured by questionnaire (such as The Lower Extremity Functional Scale (LEFS)).

Sample Size	This study is planned as a Phase 2a trial. A maximum of 12 evaluable subjects will be included in the study (6 Dercum's disease subjects and 6 lipedema subjects) and followed for as long as 56 days.
Statistical Methods	Statistical analyses will be mainly descriptive in nature where study data will be tabulated and summarized using the mean, standard deviation or standard error, median, minimum, maximum and number of subjects by cohort for continuous data. For categorical data, results will be summarized via a count and percentage by cohort. The results will be presented overall, per cohort and per cohort and dose. The effects of noncompliance, dropouts, and covariates may be assessed to determine the impact on the general applicability of results from this study. If any statistical tests are performed, they will be two-sided. The required significance level of findings will be equal to or lower than 5%. Nominal p-values will be presented. Where confidence limits are appropriate, the confidence level will be 95%. Incidence of intolerable side effects will be tabulated by study drug by cohort along with 95% confidence intervals. Change from baseline will be presented in a tabular form by visit treatment. AEs and tolerability data will be presented descriptively by treatment and cohort. AEs will be tabulated by body system, preferred term, seriousness, severity and relation to study drug by cohort. Where applicable, changes in values over time (e.g., lab values, vital signs, ECGs) will be presented; this will include clinical laboratory evaluations (including CBC, blood chemistry and urinalysis), coagulation (INR, PTT and PT), vital signs, and ECGs. Shift tables of normal / abnormal versus baseline may be presented as well. Draize scores will be presented in tabular format by visit, treatment, and cohort
Study Duration	Study duration is 2.5 months, including enrollment, treatment and follow-up period. Each subject will participate in the study for up to 42 days as part of this protocol.
Study Site	University of Arizona Medical Center, Tucson, Arizona

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

Obesity, a major health concern today, is a direct result of food-intake in excess of body energy expenditure. However, there is a vast amount of published information that proves that for some people, obesity is not the result of excessive food consumption, poor food choices, and failure to exercise (1). Problems with mitochondria, leaky lymphatics and other mutations can drive and maintain fat growth that cannot be lost through traditional diet and exercise (2). Dercum's Disease (Adiposis Dolorosa), Madelung's Disease, lipedema and Familial Multiple Lipomatosis or Angiolipomatosis are names of some of such fat disorders. These are known as Rare Adipose Disorders; they are painful, progressive disorders that result in abnormal accumulations of fat in the form of lipomas, excess lymphatic fluid, and many other symptoms.

Lipedema is a chronic condition, initially described in 1940, that occurs almost exclusively in women and manifests as symmetrical buildup of painful fat and swelling in the limbs, sparing the hands and feet (3). Fat tissue expands primarily in the lower limbs, from buttocks to ankles, as well as in the arms. Upon palpation of the fat, tiny pebbles or pea like nodules are felt. As the disease advances the nodules may increase in size and in number and may form strands of nodules(4). There are no diagnostic tools or tests for lipedema. Diagnosis of lipedema involves a clinical assessment and discussion of the individual's medical history, a process that is difficult to scale within the current healthcare system. The absence of diagnostic tools to streamline or confirm a clinical diagnosis is a key unmet need, which if addressed, has the potential to dramatically change the trajectory of the disease (5). Individuals who suffer from the disease are further impacted by the lack of public and medical awareness of lipedema, and the stigma associated with weight gain. As a result, the epidemiology of lipedema is unknown (6).

The etiology of lipedema and other types of fatty tissue enlargement is still unknown, though a genetic cause is suspected. Other possible causes of lipedema include metabolic, inflammatory, or hormonal involvement. Although the disease is reported to occur during puberty and other periods of hormonal changes, why this happens is not understood.

Lipedema is sometimes accompanied by co-morbidities, often secondary diseases, which complicate the patient's health. Psychosocial issues are prevalent in women with lipedema, contributing to health burden and complexity of disease management. The painful fat and swelling in some patients can be so debilitating that their mobility is impaired. Furthermore, many patients develop the disease alongside obesity; however, diet, exercise, and weight loss surgery have limited effect on lipedema fat.

A critical issue is the poorly understood disease, which for diagnosed patients results in limited treatment options that, at best, ameliorate the symptoms of lipedema. Early detection and treatment can significantly reduce the debilitation of the patient. Early weight and diet changes

through nutrition and exercise may be helpful in reducing non-lipedemic fat and reducing inflammation. This approach may possibly prevent the lower body from enlarging as much as it would if the patient were to become obese. However, even with strict diet and exercise regimens the disease may progress and further treatments may be necessary. While there is no proven effective treatment for lipedema, the swelling may be somewhat managed with compression garments, manual lymphatic drainage and/or Complete Decongestive Therapy. Unfortunately, some products such as garments may not be well tolerated by all patients if the patient experiences pain. Liposuction as a treatment for lipedema was developed in Germany in the late 1980s and is becoming more common. However, given the fact that liposuction is a surgery, it is not a risk-free procedure. While it has helped some patients when done by a skilled surgeon knowledgeable about lipedema, very few physicians in the United States have the knowledge and experience of physicians in Europe. Currently, different liposuction procedures (Water Assisted Liposuction [WAL] and Tumescent Liposuction [TLA]) used for lipedema patients are available but not all surgeries are suitable for all patients (7).

Dercum's disease was first described in the medical literature in 1882 by an American neurologist named Francis Xavier Dercum's. Dercum's disease is an extremely rare disorder (listed by NORD [National Organization for Rare Disorders]) characterized by multiple, painful growths consisting of fatty tissue (lipomas). These growths mainly occur on the trunk, the upper arms and upper legs and are subcutaneous. Pain associated with Dercum's disease can often be severe. Pain may be caused by these growths pressing on nearby nerves. Some individuals with Dercum's may experience swelling of various areas of the body, especially the hands. Swelling occurs for no apparent reason and often disappears without treatment. In some cases, affected individuals may also experience weight gain, depression, lethargy, and/or confusion.

The etiology of Dercum's disease is unknown, though a genetic cause is suspected (autosomal dominant). Other possible causes playing a role in the development of Dercum's disease include autoimmune disorder, disturbances in endocrine function, improper metabolism of fat and the use of high-doses of corticosteroids.

The prevalence of Dercum's disease is unknown. Dercum's disease affects females more often than males with some reports citing the disease is as 20 times more common in women. Dercum's disease can affect individuals of any age. The majority of cases are women between the ages of 45-60, especially overweight, postmenopausal women.

No specific treatment exists for Dercum's disease. Treatment is mainly symptomatic and supportive and is primarily focused on easing the characteristic painful episodes. Various analgesics have been tried with limited effectiveness. Surgical excision of fatty tissue deposits around joints may temporarily relieve symptoms although recurrences often develop. Liposuction has been used as a supportive treatment for some individuals with Dercum's disease and may provide an initial reduction in pain and improvement in quality of life (QOL) (8). These effects may lessen over time. Psychotherapy and consultation with pain management specialists may be helpful for enabling affected individuals to cope with long-term intense pain.

RZL-012 is a novel synthetic molecule enabling the conversion of white adipose tissue (WAT) into an activated thermogenic tissue at targeted anatomical sites. A single injection of RZL-012 into WAT is sufficient to trigger robust tissue remodeling. A chain of events begins with removal of WAT adipocytes by macrophages (liponecrosis), followed by an activation of remodeled cells that generate a futile cycle of ongoing energy conversion into heat. Temperature measurements of the site treated by RZL-012 reveal a persistent local increase in temperature (about 4 months in pigs). As long as these cells are active, the ensuing thermogenic tissue will consume free fatty acids (FFA) from the nearby surrounding adipose depots and further from glucose and FFA supplied via the blood stream.

The overall clinical plan for RZL-012 includes the completed exploratory (phase 0) study to evaluate the safety, thermogenesis, and pharmacodynamic response to RZL-012. An additional phase 2 study (Study RZL-012-P2aUS-001.1) in overweight and obese subjects to confirm the safety and pharmacodynamic effects of RZL-012 for the treatment of obesity will be initiated soon to explore the response to higher doses prior to the initiation of larger studies. The initial exploratory study (Study RZL-012-P0US-001.3) demonstrated that RZL-012 is well tolerated with no serious adverse events reported and that thermogenesis was evident at the injection site (abdomen) of RZL-012-treated obese subjects. Although not statistically significant (due to the initially tested low dose and a small-size study group, n=6), there was a decrease in subcutaneous fat mass (SFM) over time (compared to baseline) in the abdomen, as measured by Magnetic Resonance Imaging (MRI), in 5 out of 6 RZL-012 treated subjects, but none in vehicle treated ones.

Raziel Therapeutics believes that RZL-012 effects of adipose-tissue replacement thermogenic tissue and the ongoing lipolysis and consumption of FFA from nearby adipose tissue by the remodeled cells can be beneficial to patients with fat disorders such as lipedema and Dercum's disease. Local fat reduction and tissue remodeling at selected sites such as at the medial knee in lipedema patients and at lipomas in Dercum's disease patients may bring pain relief and improvement in QOL.

The current Phase 2a study is aimed to evaluate the safety and pharmacodynamics response to RZL-012 in lipedema and Dercum's disease patients.

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

1.2. NONCLINICAL ASSESSMENTS

1.2.1. Pharmacology

Studies in rats and pigs concluded that RZL-012 triggers remodeling of WAT to brown-like adipose tissue (BAT) tissue, thereby activating thermogenesis. The dose of RZL-012 to be used in clinical trials was extrapolated from the safety data obtained during animal testing no observed adverse effect level (NOAEL).

1.2.1.1. Efficacy In-vivo and In-vitro Studies

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

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

1. Subcutaneous or epididymal fat reduction following RZL-012 treatment.
2. Fat tissue remodeling involving non-inflammatory liponecrosis, followed by tissue "browning", where WAT is converted to BAT in rodents and smooth-muscle-like tissue in larger mammals. This conversion can be determined by:
    a. *Histological fat tissue changes:* While white adipocytes are large and resemble a single large oil drop, with a characteristic condensed nucleus, the cells of BAT are smaller, contain multiple mitochondria and a euchromatic nucleus.
    b. *Uncoupling protein 1(UCP-1) levels:* UCP-1 is a mitochondrial inner membrane protein present in BAT that can dissipate the proton gradient before it can be used to provide the energy for oxidative phosphorylation. UCP-1 normally does not exist in WAT.
    c. *Smooth-muscle-like thermogenic tissue*: In pigs, examination of tissue-sections taken from the site of injection, where robust thermogenesis was observed, revealed smooth-muscle-like histology, including typical molecular markers such as αSMA.
3. Assessment of body-surface temperature: Thermogenic tissue, e.g. classical BAT, is typified by futile burning of fatty acids (i.e., heat production instead of adenosine triphosphate [ATP]), which can be assessed utilizing infrared camera that can measure differences in body surface temperature.

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

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 (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 with an average body weight of 258.9 g, 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. It should be noted that three animals died during the post anesthesia recovery period. The cause of death was considered to be related to perioperative complications associated with the anesthesia and not related to RZL-012 or saline administration. These three animals were replaced on study. This nonclinical laboratory study was conducted in accordance with the United States Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations, 21 Code of Federal Regulations (CFR) Part 58 and the Organization for Economic Cooperation and Development (OECD) Principles on GLP [as revised in 1997; ENV/MC/CHEM(98)17]. A complete postmortem necropsy was conducted on these dead pigs, and protocol-designated tissues were saved and processed for microscopic evaluation under ambient conditions to Alizée Pathology, Thurmont, Maryland. Two of these animals were controls and one treated. Pigs are very sensitive to anesthesia and these were complications due to it. Attached is the study report - you can find mortality results and discussion on page 26-27.

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

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

A noticeable difference in subcutaneous fat temperatures was noted between treatment groups. Beginning as early as Day 4-5, an increase in temperature was noted at all test article treated sites

in both males and females. The increase in temperature was noted through Days 58-63. At study termination, subcutaneous fat temperatures at treated sites were comparable to vehicle control.

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

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

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

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

1.2.3. Additional Nonclinical Studies

- Secondary pharmacology (searching for off-target receptors).
- Establishing pharmacokinetic (PK) parameters and investigation of RZL-012 metabolism by liver enzymes and half maximal inhibitory concentration (IC_{50}) in cell-culture.
- Testing RZL-012 mutagenicity, utilizing the Ames test.
- Pyrogenicity in rabbits.
- Assessment of RZL-012 binding to the β3 receptor in cellular and nuclear receptor functional assays.

- Assessment of RZL-012 uptake by the 5-HT neurotransmitter in the absence and presence of a 5-HT2B agonist.
- Assessment RZL-012 effect on 5-HT neurotransmitter uptake and release in cellular and nuclear receptor functional assays.
- ADME-Toxicology
- Genotoxicity

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

1.2.4. Clinical Studies

Raziel Therapeutics has conducted an Exploratory phase 0, randomized, double-blind, vehicle-controlled study aimed at the evaluation of safety and thermogenesis-induction of three escalating doses of RZL-012 drug product in overweight and obese volunteers. In each cohort, 8 subjects were enrolled, 6 active and 2 control. Study design is presented in the following table:

Table 1: Phase 0 Clinical Trial Design

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

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

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

Primary Endpoints:

Safety - The primary safety endpoint was no more than two subjects experiencing a dose-limiting toxicity (DLT) event.

Efficacy - The primary efficacy endpoint was a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) infra-red thermal camera. A thermogenic effect was defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the contra-lateral (non-injected site), apparent at least 28 days after injection and non-related to inflammatory response as determined

by inflammatory cytokines. The primary efficacy evaluation was supported by results from secondary endpoints, including MRI, biopsy, and biomarkers.

Secondary Efficacy Endpoints:

1. The key secondary efficacy endpoint was the duration of the thermogenic effect in those subjects demonstrating clear thermogenesis by 28 days after injection.
2. Local reduction in fat mass as determined by MRI.
3. Clinical laboratory changes, including improvement in fasting blood glucose and lipid profile.
4. Anthropometric changes, including body weight change.
5. Establishing pharmacokinetic profile for RZL-012
6. Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site.
7. Exploration of mode of action by evaluation of inflammatory markers and cytokines

Results:

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

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

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

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

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

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

Although not statistical significant, a decrease in TC and FFA blood levels was evident in subjects of the RZL-012 treated group in cohort 3. This may imply to the mode of action of RZL-012 as stimulation of a thermogenic tissue such as BAT, is known to cause a systemic effect via the mobilization of glucose and FFA from the blood stream to feed the ongoing local thermogenesis. Thus, lipolysis of WAT triacylglycerols (TAG) stores is accelerated and the uptake of FFA derived from blood-born lipoproteins is increased due to the action of lipoprotein lipase (LPL). Raziel assumes that circulating FFA utilization by the RZL-012-induced thermogenic tissue resulted in lower levels of FFA in the blood, a process that may be beneficial for health. There was no consistent pattern to suggest a connection between inflammation markers and cytokines levels and changes in thermogenic activity reflecting the intended effect of the drug as opposed to local inflammation and distinguish between events related to M1 and M2 macrophages. Though, an increase in Adiponectin blood level was evident at Day 21 and Day 28 in 3 of 6 subjects treated with RZL-012, but not in controls. Adiponectin was found to be an obligatory mediator of cold-induced browning of WAT (9). Adiponectin can be elevated under various conditions, including those that trigger tissue remodeling in favor of thermogenesis such as chronic cold exposure. Although we do not know what triggered elevation of adiponectin in this study, it is known that downstream effects of adiponectin can promote the type of tissue remodeling we are expecting.

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

Methods and results of this exploratory study are described in the IB.

2. PURPOSE AND STUDY OBJECTIVES

2.1. PURPOSE

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 women and men with nodular Dercum's disease.

2.2. STUDY OBJECTIVES

2.2.1. Primary

The primary objective is the evaluation of the overall safety of RZL-012 following injection into the subcutaneous fat in patients with lipedema.

2.2.2. Secondary

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

3. STUDY DESIGN

3.1. DESCRIPTION OF STUDY DESIGN

This is an open label, 2 cohort, clinical trial in women with lipedema with substantial fat above the knee or women and men with nodular Dercum's disease. Each cohort will have 6 subjects who will receive RZL-012.

3.2. DOSE RATIONALE

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

Cohort 1- will be comprised of subjects with Dercum's disease. All subjects will be injected with RZL-012. Dosing will be calculated according to the size of the nodule (diameter) as determined by ultrasound: 5mg/cm^2 reaching a maximal dose of 40 mg RZL-012 per subject (1/6.25 the NOAEL based on the Human Dose Equivalent [HED] GLP Toxicology studies).

Cohort 2 - will be comprised of subjects with lipedema with substantial fat above the knee and will be conducted in a dose escalation manner.

The first 3 subjects will receive 60mg RZL-012 (1/4.688th the NOAEL based on HED from GLP toxicology study).
The last 3 subjects will receive 80mg RZL-012 (1/3.125th the NOAEL based on HED from GLP toxicology study).

3.3. DOSING

3.3.1. Dosing Regimen

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

Six subjects in cohort 1, all assigned to the RZL-012 treatment group will be dosed at a maximal dose of 40 mg RZL-012 (approximately 1/6.25th the NOAEL as determined in the GLP toxicology study). Dosing will be calculated according to the size of the nodule (diameter) as determined by ultrasound in a dose of 5mg/cm^2:

Nodule of 2-2.9cm diameter, as determined by ultrasound, will be injected 2 injections (0.1 mL each, 1 cm apart); total of 10 mg RZL-012.

Nodules of 3-3.9cm diameter, as determined by ultrasound, will be injected 3 injections (0.1 mL each, 1 cm apart); total of 15 mg RZL-012.

Nodules of 4-8cm diameter, as determined by ultrasound, will be injected 4 injections (0.1 mL each, 1 cm apart); total of 20 mg RZL-012.

Cohort 1 – Dercum's disease			
Number of Subjects – Active	6		
Nodule size – diameter (cm)	2-2.9	3-3.9	4-8
Total Dose of RZL-012 (mg)	10	15	20
Dose per NOAEL*	1/25th	1/18.75th	1/12.5th
Number of Injections	2	3	4

Six subjects in cohort 2, all assigned to the RZL-012 treatment group, will be dosed as follows:

The first 3 subjects will receive 30mg RZL-012 in 6 injections (0.1mL each) in one leg followed by 30mg RZL-012 (6 injections, 0.1mL each) in the second leg adding up to 12 injections of 60mg RZL-012 (1/4.688th the NOAEL based on HED from GLP toxicology study).

The last 3 subjects will receive 40mg RZL-012 in 8 injections (0.1mL each) in one leg followed by 40mg RZL-012 (8 injections, 0.1mL each) in the second leg adding up to 16 injections of 80mg RZL-012 (1/3.125th the NOAEL based on HED from GLP toxicology study).

*based on HED from GLP toxicology

Cohort 2 - Lipedema		
Number of Subjects – Active	2	2
Total Dose RZL-012 (mg)	60	80
Dose per NOAEL*	1/4.688	1/3.125
Number of Injections	12	16

Dosing of subjects in each cohort will progress consecutively from one individual to the other at 7-day intervals. This study design will allow the physicians to monitor safety for at least 7 days prior to dosing the next subject. For cohort 2 the decision to proceed to the next dose level will be made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject. The trial will proceed within a cohort provided that no more than one subject experiences intolerable side effects in a cohort, and based on the decision made by the Principal Investigator (PI) and the Medical Monitor.

3.3.2. Intolerable Side Effect

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

Any Grade 3 or greater event except for the following (For the following events, a discussion will be held by the PI and the Medical Monitor to decide whether considered as an intolerable side effects):

- Flu-like symptoms and fever that responds to standard treatment within 72 hours
- Localized edema and erythema
- Pruritus
- Pain
- Skin/soft tissue inflammation
- Fat Atrophy
- Liver enzymes abnormality
- Non-significant lab abnormalities, lasting less than 7 days

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

Clinical Abnormalities Table

***** Erythema – the measured local reaction at the greatest single diameter beyond the injected area surface of all injections (For Dercum's disease – nodules of 2-2.9 cm diameter 2*2 cm, nodules of 3-3.9 cm diameter 3*2 cm nodules of 4-8 cm diameter 4*2 cm. For lipedema -12*2 cm for the first subjects, 15*2cm for the following subjects and 16*2cm for the last subjects), the measurement should be recorded as a continuous variable.

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

**Induration — the measured local reaction at the greatest single diameter beyond the injected area surface of all injections (For Dercum's disease – nodules of 2-2.9 cm diameter 2*2 cm, nodules of 3-3.9 cm diameter 3*2 cm nodules of 4-8 cm diameter 4*2 cm. For lipedema -12*2 cm for the first subjects, 15*2cm for the following subjects and 16*2cm for the last subjects), the measurement should be recorded as a continuous variable.

Liver Enzyme Abnormalities Table

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

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

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

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

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

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

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINTS

The primary endpoint will be the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat in Dercum's disease and lipedema. The trial will proceed within a cohort provided that no more than one subject experiences intolerable side effects in a cohort.

4.2. SECONDARY ENDPOINTS

Following are the study's secondary endpoints:

1. For lipedema subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline as assessed by leg circumference above the knee assessments, see definition in Section 6.1.16.2.1 and by the reduction in nodules size and/or numbers assessed by ultrasound, see definition in Section 6.1.14.2.2.
2. For Dercum's disease subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline assessed by the reduction in nodules size and/or numbers by ultrasound, see definition in Section 6.1.14.2.2.
3. Extended duration of the fat reduction effect. To that end, ultrasound images and circumference measurement will be followed for 56 days, see definition in Section **Error! Reference source not found.**.
4. Elucidation of the tissue changes by ultrasound of the injection site to include reduction in fat thickness and nodular quality, see definition in Section 6.1.16.2.4.
5. Improvement in local pain as measured by Comparative Pain Scale and by the reduction in the use of analgesics, see definition in Section 6.1.16.2.4.

6. Improvement in QOL and function in lipedema subjects as measured by questionnaire (such as The Lower Extremity Functional Scale (LEFS)), see definition in Section 6.1.16.2.5.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

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

1. 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.

2. For Dercum's disease subjects – at least 2 nodules to be injected of at least 2cm diameter each, as determined by ultrasound
3. For lipedema subjects - Significant subcutaneous fat above the knee as determined by circumference of 50cm
4. Generally considered healthy according to medical history, physical examination, ECG and laboratory evaluation with a special emphasis on metabolic parameters (fasting glucose concentration < 200 mg, normal blood pressure).
5. Subjects must be able to adhere to the visit schedule and protocol requirements and be available to complete the study.
6. Subjects must sign an informed consent indicating that they are aware of the investigational nature of the study.

5.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded:

1. Unable to tolerate subcutaneous injection.
2. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator, put the subject at significant risk, are not eligible.
3. Positive blood screen for Hepatitis B surface antigen (HbSAg), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV), or positive urine screen for alcohol or drugs of abuse (unless prescribed by a physician).
4. Subjects with a clinical history of primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids are ineligible.
5. As a result of medical review, physical examination, the PI (or medically qualified nominee) considers the subject unfit for the study.
6. Known sensitivity to components of the injection formulation.
7. Prior wound, tattoo or infection in the treated area.

8. Prior invasive treatment such as surgery or injectable drug at the RZL-012 injected area.

5.3. SUBJECT IDENTIFICATION

A unique code numbers will be assigned by the investigator to the trial subject rather than the subjects' names, personal identification numbers, and/or addresses to protect the subject's identity. The code numbers and initials will be used in lieu of the subject's name when the investigator reports 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 an intolerable side effect will be withdrawn from the study, but followed until the event resolves or becomes stable. If only one subject is withdrawn or removed from the study, and no more than one subject experience intolerable side effects, then the subject will not be replaced.

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 (14 through 2 days 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, height and weight measurements at Screening Day (performed 14 through 2 days prior to baseline). Clinically significant abnormal findings except overweight and obesity should be discussed with the Sponsor.

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

6.1.5. Pain Measurement

Local pain as measured by Comparative Pain Scale (Appendix II) will be measured at Screening Day (performed 14 through 2 days prior to baseline) in order to establish a baseline to compare following drug injection. For lipedema subjects Comparative Pain Scale will be measured for each leg and for Dercum's disease subjects for each selected lipoma for injection.

Additional pain measurements will be performed on study visits Day 14, 28, and 56.

Pain will be also assessed by Subject's self-recording the daily use of analgesics in a diary. Subjects will receive a diary on Screening Day and will start recording daily painkiller use along the trial till Day 28. A week before Day 56 visit, subjects will record their daily use of

analgesics. Diaries will be checked routinely on each study visit and data will be captured in the CRFs.

6.1.6. Quality of Life and Function Measurement

QOL and function assessed by the LEFS questionnaire (Appendix III) will be measured in lipedema subjects at Screening Day (performed 14 through 2 days prior to baseline) in order to establish a baseline to compare following drug injection.

Additional pain measurements will be performed on study visits Day 14, 28 and 56.

6.1.7. Vital Signs Measurements

Subjects' vital signs will be measured at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria.

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

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

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

6.1.8. Serology Assays

Assays for HCV, HbSAg, and HIV will be conducted at Screening Day 1 (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria.

6.1.9. Clinical Laboratory Tests

Clinical laboratory tests will be conducted at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria. Additional studies will be conducted on different study visits according to schedule as written below. The maximum total blood volume will be 30 mL per visit. Every out-of-range value will be assessed by a physician and deemed as either clinically significant or clinically not significant. Values that represent a change from baseline in subject’s medical status according to the laboratory normal ranges will be adequately documented as an AE as described in Section 9.

6.1.9.1. Hematology

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

Hematology tests will include Complete blood count (CBC) (including White blood cells [WBC] differential values) and coagulation tests: White blood cells (WBC), Red blood cells (RBC), Hemoglobin, Hematocrit, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Red cell distribution width (RDW), Platelets, Mean platelet volume (MPV), Fibrinogen, International normalized ratio (INR), Partial thromboplastin time (PTT) and Prothrombin time (PT).

6.1.9.2. Serum Chemistry Analysis

Testing of blood chemistry values will be conducted at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria.

Additional Serum Chemistry testing will be conducted at Day 0 (before injection), 24hr ± 2hr following injection and on study visit Day 3, 7, 14 and 28.

Serum chemistry will include: Sodium, Calcium, Potassium, Phosphorus, Glucose, Liver enzymes (AST, ALT, Lactate dehydrogenase [LDH], Creatine-kinase MM [CK-MM], Gamma-glutamyltransferase [GTTP], Alkaline phosphatase [ALP]), Bilirubin, Creatinine, BUN, Total protein, Albumin, Amylase, Creatine phosphokinase [CPK], C-reactive protein [CRP]).

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

6.1.9.3. Urine Drug Screen

Urine drug screen will be conducted at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study exclusion criteria.

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

6.1.9.4. Urinalysis

Urinalysis will be conducted at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria and to allow differential diagnosis in case of urinary tract associated AE. Additional urinalysis testing will be conducted on study visit Day 14 and 28.

Urinalysis will include: Nitrite, Sodium, Potassium, Calcium, Phosphate, Protein, Red blood cells (RBC), WBC, Blood, Glucose, Ketone bodies, Bilirubin, Urobilirubin, Urine specific gravity, Osmolality, and pH.

6.1.10. ECG

Subjects' ECG will be performed at Screening Day (performed 14 through 2 days prior to baseline) in order to ensure compliance with study inclusion criteria. ECG is to be performed on at least a triplicate of heartbeats for all measurements and will be recorded at a speed of 25 mm/sec. Additional ECGs will be performed at 4h ± 30min, 8h ± 30min and 24h ± 2h following drug injection (Day 0-1) and on Days 14 and 28.

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

6.1.11. Draize Score

Subjects' skin irritancy will be evaluated by Draize score at Screening Day (performed 14 through 2 days prior to baseline) in order to establish a baseline to compare following drug injection. For lipedema subjects evaluation of Draize score will be performed for each leg and for Dercum's disease subjects for each selected lipoma for injection.

Additional skin irritancy evaluation to assess subject's safety will be performed at baseline visit prior to injection, and on 2h ± 30min following injection, on the following day 24h ± 2h after drug injection and on study visits Day 7, 14, 21, 28 and 56.

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

6.1.12. Photography of the Injected Site

Documentation of the skin condition and fat reduction effect in the injected area will be conducted at Screening Day (performed 14 through 2 days prior to baseline). Additional

photography will be performed at Day 1 (24h ± 2h following drug injection) and on study visits Day 7, 14, 21, 28 and 56.

Photography with a digital camera will include:

1. For Dercum's disease – Each of the injected site
    a. A picture from above
    b. A side picture

For each lipoma, the distance away from the lipoma with the best view of the skin will be recorded and fixed throughout the study to assess lipoma size changes.

2. For lipedema
    a. Both sites above the knees
    b. Sites of each knee separately
    c. A side picture of each knee

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

6.1.13. Leg Circumference

Leg circumference measurement will be conducted at Screening (performed 14 through 2 days prior to baseline) to ensure compliance with study inclusion criteria and at Day 0 (before injection) to establish a baseline. Additional leg circumference measurements will be performed on Day 28 and 56.

The subject will be instructed to remove all garments from the legs and stand upright barefoot. The technician will stand on the subject's side and will palpate the knee area to locate the suprapatellar fat. If there is no excess to the suprapatellar fat measure 4-6 cm from the knee. With a cosmetic pencil, draw a horizontal line and record its distance from the floor. Extend the measuring tape around the leg. Position the tape in a horizontal plane at the level of the measurement mark. Check that the tape sits parallel to the floor and lies snug but does not compress the skin. Always position the zero end of the tape below the section containing the measurement value. Take the measurement in centimeters to the nearest 0.1 cm (one digit after the decimal point). The technician will take three measurements of leg circumference. When the measurement is measured the same twice (±0.5cm), that measurement will be used. If measurement are taken and all three are different, a fourth measurement will be taken until the same measurement is achieved twice.

6.1.14. Imaging: Ultrasound (US)

Evaluation of Ultrasound (Vevo 2100 or 3100 with transducers at 20, 50 or 70 mHz; or Esaote MyLab Gamma Ultrasound System with 20 mHz transducer) will be conducted at Screening

(performed 14 through 2 days prior to baseline) to ensure compliance with study inclusion criteria and establishing a baseline. For Dercum's disease subjects - nodule size and quality will be assessed, for lipedema subjects – nodular size (if applicable), nodular quality and fat thickness will be assessed. Additional US will be performed on Day 28 and 56.

Nodular quality for Dercum's subjects will be assessed according to the following parameters: capsule visibility, hyperechoic or hypoechoic tissue, reverse starry sky (small black dots all over consistent with angiolipoma), flurry or snowstorm appearance, location measured to the skin and vascularity internal or around the lipoma.

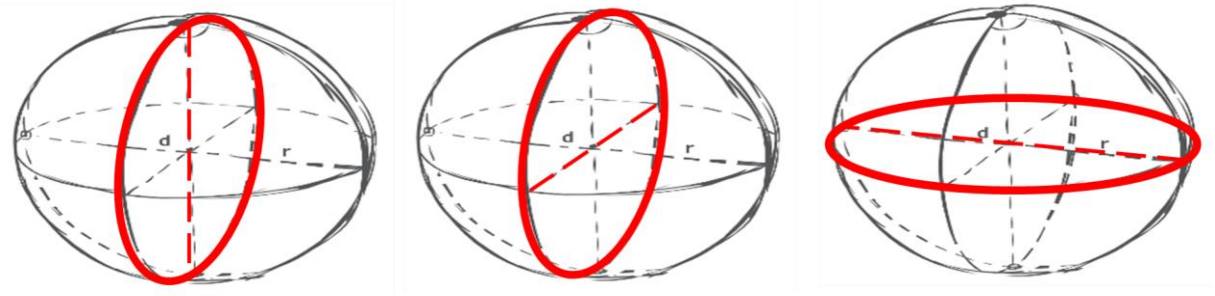
Nodular quality for lipedema subjects will be assessed according to the following parameters: hyperechoic or hyperechoic tissue, flurry or snowstorm, internal hypoechoic rounded area consistent with a vessel and distance from skin.

Additional ultrasound imaging will be conducted at Day 0 (before injection):

- For Dercum's disease subjects - nodule size evaluation to ensure proper dose injection. The selected nodules for injection will be marked in circles with a non-erasable pen. This mark should be strengthened on every visit.

Assessment of nodular size will be by diameter (mm) and surface (mm^2) in three dimensions as illustrated below:

- Height
- Width
- Length



- **Height** **Width** **Length**

- For lipedema subjects – assessment of presence of nodules to be injected along the horizontal plane 4-6 cm in the suprapatellar fat. The selected nodules for injection will be marked in circles with a non-erasable pen. This mark should be strengthened on every visit. If no nodules are noted in the horizontal plane, drug will be injected in to the fatty tissue and in this case small nodules seen in ultrasound will be followed for changes.

6.1.15. Adverse Events

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

The trial will proceed within a cohort and from one cohort to the next as long as no more than one subject experiences intolerable side effects and based on the decision made by the PI. Proceeding from one subject to the next will be based on the decision made after reviewing all safety data collected by Day 7 within 2 ± 1d of the last dosed subject in each cohort.

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. In addition, the following information regarding the AE must be obtained: AE description, start date, end date (if applicable) or ongoing, severity, seriousness, relationship to study drug, outcome (e.g., resolved / unresolved), and action taken (e.g., concomitant medication). The sponsor or the sponsor representative will provide information regarding serious adverse event (SAE) expectedness based on data included in the IB. AE monitoring will be conducted throughout subject's participation up to 56 days after injection.

6.1.16. Evaluation of Response

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

6.1.16.1. Evaluation of Primary Endpoints

6.1.16.1.1. Safety and Tolerability Monitoring

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

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

1. AEs and SAEs, including severity, relation to study treatment and classification by whether or not these events comprise intolerable side effects.
2. Physical exams, Draize score and vital signs measurements.
3. Urine testing.
4. Blood laboratory testing for changes in hematology and chemistry values.
5. ECG

6. Subjects questioning - full medical history during screening, routine AE reporting, tolerability monitoring and through review of subject's analgesics use diary.

6.1.16.2. Evaluation of Secondary Endpoints

6.1.16.2.1. Local Fat Reduction for Lipedema Subjects

For lipedema subjects, local reduction in fat mass will be evaluated by measurement of the circumference of the leg above the knee. A local fat reduction is defined as a reduction (compared to baseline) in the circumference of the leg above the knee.

6.1.16.2.2. Local Fat Reduction

Local fat reduction in all subjects will be evaluated by ultrasound. Local fat reduction is defined as the reduction in nodules size and/or numbers in the injected area as compared to baseline. Ultrasound will be evaluated in all subjects at baseline and at Day 28.

6.1.16.2.3. Duration of the fat reduction effect

The duration of the local fat reduction in all subjects will be evaluated by ultrasound and by leg circumference above the knee in lipedema subjects at Day 56 compared to baseline and to Day 28.

6.1.16.2.4. Tissue Changes

Tissue changes will be evaluated by ultrasound. Tissue changes are defined as changes in fat thickness and nodular quality at Day 28 and Day 56 as compared to baseline.

6.1.16.2.5. Improvement in Local Pain

Improvement in local pain will be assessed by Comparative Pain Scale and by reduction in the use of analgesics (dose and/or times a day) by Day 28 and Day 56 with comparing to baseline.

6.1.16.2.6. Improvement in Quality of Life and Function

Improvement in QOL and function in lipedema subjects as measured by questionnaire (such as LEFS) by comparing to baseline at Day 28 and Day 56.

6.1.16.3. 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.
- Completion of analgesics use diary by the subject.

6.1.16.4. 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).

6.1.16.5. 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 no later than 2 days prior to baseline visit for all 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
- Pain Measurement – Section 6.1.5
- QOL Measurement –Section 6.1.6
- Vital Signs and Measurements - Section 6.1.5
- Serology Assays – Section 6.1.8
- Clinical Laboratory Tests - Section 6.1.9
- ECG - Section 6.1.10

- Draize Score – Section 6.1.11
- Photography of Injected Site – Section 6.1.12
- Leg Circumference – Section 6.1.12
- Ultrasound – Section 6.1.12

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

6.2.2. Study Randomization

This is an open label study where all subjects will receive the investigational drug (RZL-012).

6.2.3. Study Treatment

6.2.3.1. Treatment with RZL-012 Investigational Therapy

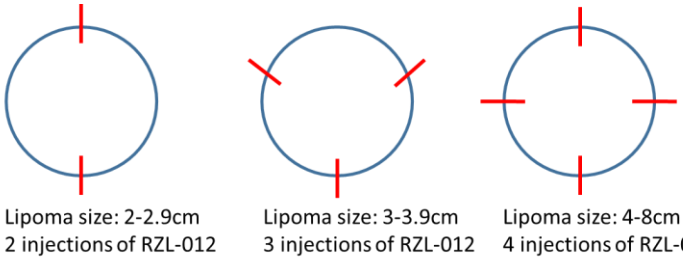
RZL-012 is an investigational product supplied as a single dose single treatment injection in multiple sites (2-16) of injections. Before injection, subjects will be advised to keep their regular diet and physical activity.

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

The hole of the needle should be pointing into the fat layer and the injection direction should be towards 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 viscose, therefore resistance is expected while injecting.

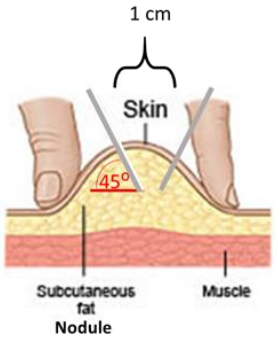
For Dercum's disease - The 1st cohort will be comprised of subjects with Dercum's disease. Subjects will receive a single treatment in multiple sites (2-8) according to the design below Figure 2).

Figure 1: RZL-012 Injection Design in Dercum's Disease Subjects



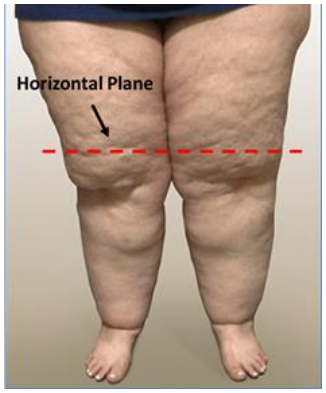
Injections will be diagonally (45 °) to the skin surface towards the center of the nodule and the distance between injections in a nodule will be 1 cm (Figure 2).

Figure 2: RZL-012 Injection Sites in Dercum's Disease Subjects



For Lipedema - The 2nd cohort will be comprised of subjects with lipedema with substantial fat above the knee. A grid line will be drawn with a makeup pencil in a horizontal plane (Figure 3) 4-6 cm from the suprapatellar fat and its distance from the floor recorded. An attempt should be made to find palpable nodules along the grid line. The injection sites will be marked in circles with a non-erasable pen. This mark should be intensified upon following visits. Injections will be given in multiple sites (4-8 in each leg), diagonally (45 °) to palpable nodules, in the fat above the knee. An attempt should be made to lift the nodule and inject into the middle of the fat-mass. If no nodules are noted in the horizontal plane, drug will be injected into the fatty tissue (in this case small nodules seen in ultrasound will be followed for changes). Injections will be on the same horizontal plane.

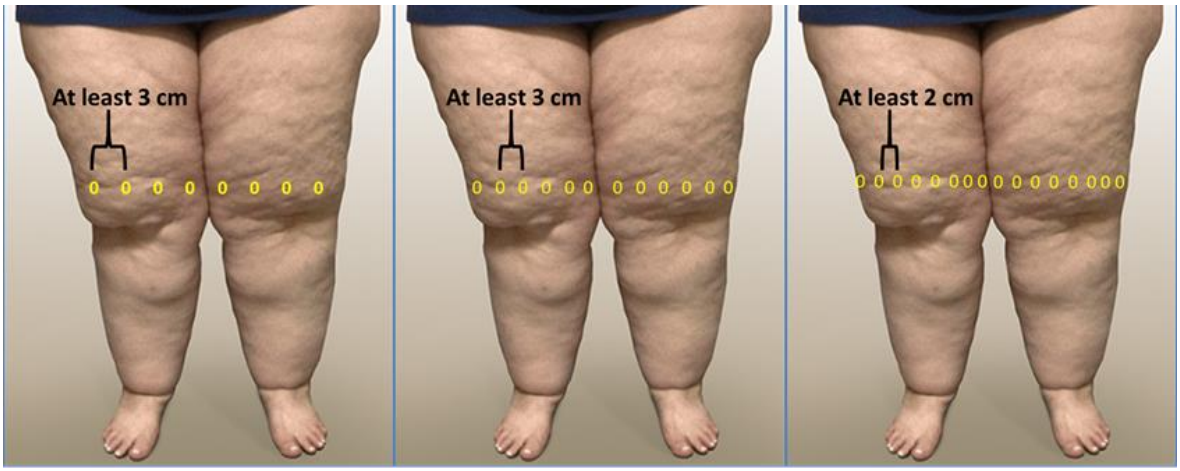
Figure 3: RZL-012 Injection in Lipedema



Injections will be spread as much as possible along the grid line and the distance between injected sites (Figure 4) will be:

- At least 3 cm - For subjects receiving 8 and 12 injections.
- At least 2cm - For subjects receiving 16 injections.

Figure 4: RZL-012 Injection Sites in Lipedema Subjects



In lipedema subjects study will be performed in a dose escalation manner:

The first 2 subjects will receive 20mg RZL-012 in 4 injections (0.1mL each) in one leg followed by 20mg RZL-012 (4 injections, 0.1mL each) in the second leg adding up to 8 injections of 40mg RZL-012 (1/6.25th the NOAEL based on HED from GLP toxicology study).

The next 2 subjects will receive 30mg RZL-012 in 6 injections (0.1mL each) in one leg followed by 30mg RZL-012 (6 injections, 0.1mL each) in the second leg adding up to 12 injections of 60mg RZL-012 (1/4.688th the NOAEL based on HED from GLP toxicology study).

The last 2 subjects will receive 40mg RZL-012 in 8 injections (0.1mL each) in one leg followed by 40mg RZL-012 (8 injections, 0.1mL each) in the second leg adding up to 16 injections of 80mg RZL-012 (1/3.125th the NOAEL based on HED from GLP toxicology study).

Within each cohort, dosing of the subjects will progress consecutively from one individual to the other with a minimum of 7-days between subjects to assess safety. This study design will allow the physicians to monitor safety for at least 7 days prior to dosing the next subject. For cohort 2 the decision to proceed to the next dose level will be made after reviewing all safety data collected by Day 14 within 2 ± 1d of the last dosed subject. The trial will proceed within a cohort provided that no more than one subject experiences intolerable side effects in a cohort, and based on the decision made by the PI and the Medical Monitor.

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 baseline study visit.

6.2.4. Baseline Visit

Baseline visit is defined in the study as Day 0. Baseline visit will be performed to complete screening evaluation, and to review all procedures necessary to confirm subject eligibility. Subjects will stay under supervision in the study center till 8h + 3h following drug injection.

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

Table 2: Subject Information and Timeframes

Information	Timeframe	Follow-up Timeframe
Informed Consent Form	Signed prior to any study dedicated procedure	
Medical History and Concomitant Medications	At Screening Day visit	
Physical examination	At Screening Day visit and at Day 28	
Pain Measurement	At Screening Day visit and at Days 14, 28	At Day 56
QOL Measurement in lipedema subjects	At Screening Day visit and at Days 14, 28	At Day 56
Vital Signs	At Screening Day visit and at Days 0 (pre and following injection), 1, 7, 14, 21, 28	
Pulse rate	At Day 0 (following injection) and at Day 1	
ECG	At screening Day 1 visit, at Day 0 (following injection) and at Days 1, 14, 28	
Draize Score at the Injected Site	At Screening Day and at Days 0 (pre- and following injection), 1, 7, 14, 21, 28	At Day 56
Serology assays (HbSAg, HCV and HIV)	At Screening Day visit	
Drug screen	At Screening Day visit	
Serum chemistry and Hematology	At Screening Day and at Day 1, 3, 7, 14 and 28	
Urinalysis	At Screening Day visit and at Days 14 and 28	

Information	Timeframe	Follow-up Timeframe
Ultrasound for nodules quality and size. Fat thickness – for lipedema	At Screening Day visit and at Day 28	At Day 56
Ultrasound for nodules size and selection for injection	At Days 0 (pre- injection)	
Photography of the Injected Sites	At Screening Day visit and at Days 1, 7, 14, 21, 28	At Day 56
AE Assessment	At Days 1, 3, 7, 14, 21, 28	At Day 56

6.2.5. Subject Site Visits

Subject site visits will be performed ± 1 day from scheduled date. All data relevant for the visit needs to be obtained within 3 days (e.g., blood tests) of visit.

Subject sites visits will include procedures as described in Appendix I.

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

6.2.6. Termination Visit

Once study is discontinued, all reasonable measures should be taken to perform a termination visit. Termination visit should include all procedures necessary to complete subjects' records: AE reporting, any clinical laboratory test needed to evaluate unresolved AEs, evaluation of response, recovery of all clinical supplies and compliance diaries, and updating of subject contact information. An effort should be made to perform all activities conducted on visit Day 28.

6.2.7. Unscheduled Visit

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

7. SAFETY CONSIDERATIONS AND GUIDANCE FOR INVESTIGATORS

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

7.1. STUDY RESTRICTIONS REGARDING CONCOMITANT MEDICATIONS

Subjects may not receive the following medications while on study:

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

Before dosing, analgesic gels such as Lidocaine (e.g., Emla) or Pramoxine should be used to numb the injected site. An ice pack may be applied on the site of injection following dosing to help reduce pain. At day 1 following injection application of the anti-histamine Benadryl Gel (Diphenhydramine hydrochloride 1 %for topical use only) should be initiated prophylactically, according to drug instructions for use, to avoid itching at the injected area. Benadryl Gel should be applied for 7 days.

Use of nattokinase is prohibited and the use of other supplements or complementary medicines/botanicals should be approved by the PI, except for conventional multivitamin supplements. The use of prohibited supplements should be stopped a week before injection.

7.2. SAFETY MEASUREMENTS

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

- Any injection site reaction may occur. Pain, swelling, itching, edema, erythema, hematoma, etc.
- Slight transient injection site bleeding following injection may occur.
- Itching in the injected area may occur, and study subjects should be advised to use an antihistamine gel for topical use according to drug recommendations, wear wide cotton shirts, prevent touch with irritable clothing, avoid scratching and avoid exposure to direct sun. Itching is expected till 7 days following drug injection.
- Local erythema in the injected area.
- Local heat in the injection area.
- Study restrictions regarding concomitant medications are listed in Section 7.1.
- The local subcutaneous fat reduction may appear as a slight dip in the skin surface. This decline may be temporary and transient.

- Transient increase (72%) in the WBC count by 24 hours following injection, which returned to basal level after 14 days. Probably associated with the inflammatory response at the site of injection and involve neutrophils, monocytes and eosinophils.
- Increased level of BUN and of creatinine and minimal single cell necrosis was observed in tubular epithelium at cortico medullary junction of kidney in rats receiving a dose 25 times the highest dose in this study. All abnormalities were found to be reversible by Day 14.
- Increased AST level which is most typical of myofiber injury associated with study related procedures. This elevation was found to be reversible by Day 14.
- Transient increase of serum CRP levels (in rats) which returned to the basic level by 14 days.
- Marked irritancy in the injected subcutaneous tissue resulting in coagulation necrosis of relatively large areas in the subcutaneous tissue planes acutely. Necrosis persisted for up to 14 days and was accompanied by early evidence of healing in the form of chronic inflammation and fibrosis.
- Local inflammation (minimal to moderate) with muscle degeneration, epidermal/dermal necrosis (minimal to severe) and parakeratosis (minimal). Inflammation observed at injection site was also extended to adjacent subcutaneous adipose tissue (SAT). By 56 days the inflammation was minimal, muscle degeneration was not evident and inflammation to adjacent SAT was present.
- A slight elevation in body temperatures was noted in male pigs.
- Sinus tachycardia (in pigs), occurring at the 4 hour interval post dosing.
- In addition, other acceptable treatment to relieve drug-related AE's should be used at Investigator's discretion.

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

- At the injection site -local and transient: erythema, edema, pruritus, anesthesia, pain, mass (subcutaneous scar).
- Abdominal abscess
- Transient moderate to severe elevation of the liver enzymes: ALT and AST.

7.3. PREMATURE DISCONTINUATION FROM STUDY

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

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

- Other reasons regarded by PI as warranting subject's discontinuation.
- Premature study termination as described in Section 7.4.

Subjects who discontinue the study prematurely will be queried whether an 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 for a single dose in multiple injections into the subcutaneous fat. The injection dosing regimen and technique is crucial for the therapy safety and efficacy.

8.2. FORMULATION, PACKAGING AND LABELING

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

8.3. STORAGE AND STABILITY OF RZL-012 AND VEHICLE

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

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

The storage conditions are summarized in Table 3.

Table 3: RZL-012 Storage Conditions

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

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

8.4.1. Dosage

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

8.4.2. Administration and Instructions for Use

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

The vial should be manually shaken before consumption.

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

- Cohort 1 - Dercum's disease subjects:

  Nodule of 2-2.9cm diameter -will be injected 2 * 0.1 mL/syringe/nodule

  Nodules of 3-3.9cm diameter - will be injected 3 * 0.1 mL/syringe/ nodule

  Nodules of 4-8cm diameter - will be injected 4 * 0.1 mL/syringe/ nodule

  In total -A maximum of 8* 0.1 mL/syringe/subject.

- Cohort 2 - lipedema subjects:

  First 3 subjects: 6*0.1 mL/syringe/leg, a total of 12* 0.1 mL/syringe/subject.

  Last 3 subjects: 8*0.1 mL/syringe/leg, a total of 16* 0.1 mL/syringe/subject.

One vial may 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 was done 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 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 June 14, 2010) (10).

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

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

9.3. CAUSALITY ASSESSMENT OF ADVERSE EVENTS

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

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

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

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

Table 4: Definition of Causality

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

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

*In this protocol, Unlikely is deemed as Unrelated.

9.4. UNEXPECTEDNESS OF ADVERSE DRUG REACTIONS

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

9.5. ADVERSE EVENT REPORTING AND MONITORING REQUIREMENTS

9.5.1. General

All AEs, serious and non-serious, will be fully documented in both source documents and CRFs as described in Section 6.1.13, 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 (28 days after the injection of RZL-012 and in the highest dose cohort until 6 months from injection of RZL-012), should be captured in the CRF. AEs should be recorded in the CRF using the medical terminology found in the source documentation. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology.

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

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

9.5.2. SAE Reporting

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

Sponsor contact details for SAE reporting:

Racheli Gueta, Rachel.gueta@raziel-therapy.com, fax: 972-2-625-0901.

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

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

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

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

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

9.5.3. Expedited Reporting

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

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

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

Such events must be reported within one (1) working day of the investigator becoming aware of the event. Pregnancies shall be followed for the duration of the pregnancy. It is the PI's

responsibility to provide to the Sponsor follow-up information on the outcome of the pregnancy including information about any sequelae.

10. STATISTICAL CONSIDERATIONS

10.1. STUDY DESIGN AND OBJECTIVE

This is an open label, 2 cohort, clinical trial in women with lipedema with substantial fat above the knee or women and men with nodular Dercum's disease. Each cohort will have 6 subjects who will receive RZL-012.

- The 1st cohort will be comprised of subjects with Dercum's disease
- The 2nd cohort will be comprised of subjects with lipedema with substantial fat above the knee.

Primary objective: Evaluation of the overall safety of RZL-012 following injection into the subcutaneous fat in patients with lipedema.

Secondary objective: Evaluation of 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.

10.2. STUDY ENDPOINTS

10.2.1. Primary Safety Endpoints

The primary safety endpoint is the incidence of intolerable side effects and AEs.

10.2.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- For lipedema subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline based on ultrasound (reduction in nodules size and/or numbers) and leg circumference above the knee assessments.
- For Dercum's disease subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline based on ultrasound (reduction in nodules size and/or numbers).
- Extended duration of the fat reduction effect. To that end, ultrasound images and above the knee circumference measurement will be followed for 56 days.
- Elucidation of the tissue changes by ultrasound of the injection site to include reduction in fat thickness and nodular quality.

- Improvement in local pain as measured by Comparative Pain Scale and by the reduction in the use of analgesics.
- Improvement in QOL and function in lipedema subjects as measured by questionnaire (such as LEFS).

10.2.3. Safety and Tolerability Endpoints

Safety endpoints include:

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

10.3. SAMPLE SIZE JUSTIFICATION

This study is planned following a 6 subjects per group paradigm. A maximum of 12 evaluable subjects will be included in the study (6 subjects with Dercum's disease and 6 subjects with lipedema) and followed for as long as 2 months.

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 at least one 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 analysis will be performed using SAS V9.3 or higher (SAS Institute, Cary NC, USA).

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

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

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

10.5.2. Subject Disposition

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

Note that the actual study duration is for a period of maximum 2 months, with efficacy analyses being conducted at 28 days and 56 days.

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

10.5.5. Efficacy Analysis

Percent changes from baseline in local fat reduction (circumference of the leg above the knee, nodules size and/or numbers in the injected area) and tissue changes (fat thickness), will be presented in tabular form by visit.

Changes in nodular quality, local pain, quality of life and function will be presented in tabular form by visit and cohort.

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 (V19.1 or higher) treatment.

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

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

10.6. HANDLING OF MISSING DATA

No imputation of missing data will be performed.

10.7. INTERIM ANALYSIS

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.

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

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

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

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

11.2. RECORD KEEPING

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

11.3. SOURCE DATA AND SOURCE DOCUMENTS

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

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

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

- Subjects' 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. 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

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Appendix I: Trial Schedule of Events

Study Procedure	**Screening Day**	**Baseline (Treatment)**		**Visit Schedule (Days 1 to 28)**			
Study Day[a]	**Day[a]-(-14) through Day (-2)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**
Signed informed consent	X						
Medical history	X						
Concomitant Medication	X						
Complete physical exam	X						
Pain measurement	X					X	
For lipedema subjects - QOL measurement	X					X	
Serology assays (HbSAg, HCV, HIV)	X						
Urine Drug Screen	X						
Height and weight	X						
For Dercum's disease subjects – ultrasound assessing nodules size (diameter) and quality	X						
For lipedema subjects – assessing fat thickness and nodular quality by ultrasound.	X						
For lipedema subjects – measurement of leg circumference above the knee	X	Pre [c] X					
For lipedema subjects – ultrasound assessing nodules to be injected		Pre [c] X					
For Dercum's disease subjects – ultrasound re-assessing nodules size		Pre [c] X					
Photography of site of injection	X		X		X	X	X
Serum Chemistry, Hematology [b]	X	Pre [c] X	X	X	X	X	
Urinalysis	X					X	
Draize score at the injected site [d]	X	Pre [c] X post [c]	X		X	X	X
Vital signs [e]	X	Pre [c] X post [c]	X		X	X	X
Injection of RZL-012		X					
ECG [f]	X	X post [c]	X			X	
Pulse rate [g]		X post [c]	X				
Subjects diary recording of analgesics use	X	X	X	X	X	X	X
AE assessment			X----------				

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

b. CBC, coagulation, serum chemistry analysis, renal and liver function, urinalysis, CPK, amylase measurement: before injection,14d and 28d following injection
c. Pre/post – refers to before/after injection respectively
d. Draize score evaluation: before injection, 2h, 24h and 7d, 14d, 21d and 28d following injection
e. Vital signs measurement: before injection, 2h, 24h and 7d, 14d, 21d and 28d following injection
f. ECG is to be performed in triplicate for all measurements in given time point: 4h, 8h, 24h following injection
g. Pulse rate measurements at given time points: 1h, 2h, 4h, 8h, 24h following injection in the opposite hand of blood sampling

Appendix II: Comparative Pain Scale

Comparative Pain Scale		
	0	No pain. Feeling perfectly normal.
Minor Does not interfere with most activities. Able to adapt to pain psychologically and with medication or devices such as cushions.	1 Very Mild	Very light barely noticable pain, like a mosquito bite or a poison ivy itch. Most of the time you never think about the pain.
	2 Discomforting	Minor pain, like lightly pinching the fold of skin between the thumb and first finger with the other hand, using the fingernails. Note that people react differently to this self-test.
	3 Tolerable	Very noticable pain, like an accidental cut, a blow to the nose causing a bloody nose, or a doctor giving you an injection. The pain is not so strong that you cannot get used to it. Eventually, most of the time you don't notice the pain. You have *adapted* to it.
Moderate Interferes with many activities. Requires lifestyle changes but patient remains independent. Unable to adapt to pain.	4 Distressing	Strong, deep pain, like an average toothache, the initial pain from a bee sting, or minor trauma to part of the body, such as stubbing your toe real hard. So strong you notice the pain all the time and *cannot completely adapt*. This pain level can be simulated by pinching the fold of skin between the thumb and first finger with the other hand, using the fingernails, and squeezing real hard. Note how the similated pain is initially piercing but becomes dull after that.
	5 Very Distressing	Strong, deep, piercing pain, such as a sprained ankle when you stand on it wrong, or mild back pain. Not only do you notice the pain all the time, you are now so preoccupied with managing it that you normal lifestyle is curtailed. Temporary personality disorders are frequent.
	6 Intense	Strong, deep, piercing pain so strong it seems to partially dominate your senses, causing you to think somewhat unclearly. At this point you begin to have trouble holding a job or maintaining normal social relationships. Comparable to a bad non-migriane headache combined with several bee stings, or a bad back pain.
Severe Unable to engage in normal activities. Patient is disabled and unable to function independently.	7 Very Intense	Same as 6 except the pain completely dominates your senses, causing you to think unclearly about half the time. At this point you are effectively disabled and frequently cannot live alone. Comparable to an average migraine headache.
	8 Utterly Horrible	Pain so intense you can no longer think clearly at all, and have often undergone severe personality change if the pain has been present for a long time. Suicide is frequently contemplated and sometimes tried. Comparable to childbirth or a real bad migraine headache.
	9 Excruciating Unbearable	Pain so intense you cannot tolerate it and demand pain killers or surgery, no matter what the side effects or risk. If this doesn't work, suicide is frequent since there is no more joy in life whatsoever. Comparable to throat cancer.
	10 Unimaginable Unspeakable	Pain so intense you will go unconscious shortly. Most people have never experienced this level of pain. Those who have suffered a severe accident, such as a crushed hand, and lost consciousness as a result of the pain and not blood loss, have experienced level 10.

Appendix III: Lower Extremity Functional Scale

Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
1 Any of your usual work, housework, or school activities.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2 Your usual hobbies, re creational or sporting activities.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3 Getting into or out of the bath.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4 Walking between rooms.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

5 Putting on your shoes or socks.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6 Squatting.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7 Lifting an object, like a bag of groceries from the floor.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8 Performing light activities around your home.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9 Performing heavy activities around your home.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10 Getting into or out of a car.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11 Walking 2 blocks.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
12 Walking a mile.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
13 Going up or down 10 stairs (about 1 flight of stairs).	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
14 Standing for 1 hour.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
15 Sitting for 1 hour.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
16 Running on even ground.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
17 Running on uneven ground.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
18 Making sharp turns while running fast.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
19 Hopping.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
20 Rolling over in bed.	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Source: Binkley et al (1999): The Lower Extremity Functional Scale (LEFS): Scale development, measurement properties, and clinical application. Physical Therapy. 79:371-383.