RZL-012 Study Protocol

Protocol Number RZL-012-DD-P2bUS-001

A Double Blind, Randomized, Multi-Center, Placebo-Controlled Phase 2B Clinical Trial for the Evaluation of Efficacy and Safety of RZL-012 in Subjects having Dercum's Disease Lipomas.

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LIST OF ABBREVIATIONS

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

STATEMENT OF COMPLIANCE

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

INVESTIGATOR SIGNATURE PAGE

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

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

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

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

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

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

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

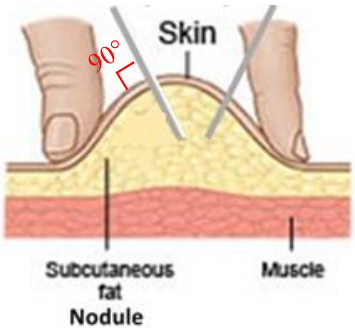
PROTOCOL SYNOPSIS

Protocol Number	RZL-012-DD-P2bUS-001
Protocol Title	A Double Blind, Randomized, Multi-Center, Placebo-Controlled Phase 2B Clinical Trial for the Evaluation of Efficacy and Safety of RZL-012 in Subjects having Dercum's Disease (DD) Lipomas.
Study Phase	Phase 2b
Study Drug	RZL-012
Study Objectives	Primary objective: Evaluation of the efficacy of RZL-012 following injection into lipomas/nodules of Dercum's Disease (DD) subjects. Efficacy will be determined by ultrasound assessment of the lipoma/nodule dimensions after treatment vs baseline. Secondary objective: Assessment of lipoma/nodule associated pain using the Comparative Pain Scale. Safety will be assessed by frequency of adverse events and by change-from-baseline values for vital signs, clinical laboratoryand ECG. Exploratory objective: Improvement in Quality of Life – QOL questionnaire
Study Design	This is a double blind, multi-center, randomized, placebo-controlled clinical trial in DD subjects having lipomas. Subjects will be randomized in a 1:1 ratio into either the RZL-012 or the placebo arm. Once the study ends and codes are opened, 84 days after dosing, placebo-treated subjects will be offered the option of receiving treatment with RZL-012. Subjects who choose this will be followed up for an additional 84 days. At least 4 lipomas/nodules, preferably 6, and no more than 8, will be injected per subject. Dosing will be according to lipoma size, where the total injected dose will not exceed 240 mg per patient (48 injections of 5mg/injection).
Study Population	Women and men, 18- 70 years old, diagnosed with DD having lipomas
Main Inclusion Criteria	Subjects must meet all the following to be eligible for study participation: 1. Women and men, 18- 70 years old. 2. At least 4 painful lipomas of appropriate size to be injected on a background of DD. 3. Generally considered healthy according to medical history, physical examination, electrocardiogram (ECG) and laboratory evaluation with an emphasis on metabolic parameters (fasting glucose concentration < 200 mg/dL). 4. Subjects must be able to adhere to the visit schedule and protocol requirements and be capable of completing the study. 5. Males or females in the age of fertility are willing to refrain from sexual activity or agree to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012. 6. Subjects must sign an informed consent indicating they are aware of the investigational nature of the study.

<table>
<tr><td>Main Exclusion Criteria</td><td>Subjects meeting any of the following criteria will be excluded:
1. Unable to tolerate subcutaneous injections.
2. Pregnant women.
3. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator places the subject at significant risk.
4. Positive blood screen for Hepatitis B surface antigen (HbSAg), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV).
5. Subjects with a clinical history of active primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids
6. Subjects with dysfunctional gallbladder activity, e.g. underwent cholecystectomy or cholecystitis.
7. As a result of medical review and physical examination, the PI (or medically qualified nominee) considers the subject unfit for the study.
8. Known sensitivity to components of the injection formulation.
9. Prior wound, tattoo or infection in the treated area.
10. Prior invasive treatment such as surgery or injectable drug at the RZL-012 injected area.
11. Subjects treated chronically at least 3 months prior to study entry with systemic steroids or immunosuppressive drugs.
12. Subjects treated chronically at least one week prior to study entry with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
13. Current participation or participation within 3 months prior to the start of this study in a drug or other investigational research study.</td></tr>
<tr><td>Study Drug Dosage and Administration</td><td>RZL-012 is a solution of 50 mg/ml RZL-012 in a vehicle comprised of water, propylene glycol and surfactant. Placebo is a solution comprised of vehicle only. Each injection of RZL-012 and placebo contains 0.1 ml.
<u>Placebo-Controlled Phase:</u>
Subjects will be randomized to receive either RZL-012 or vehicle in a ratio of 1:1. Subjects will receive their study treatment on a single occasion. Dosing will be calculated according to lipoma size (diameter) as determined by ultrasound:
The table below presents the dosages according to lipoma size:

<table>
<tr><td>Number of Subjects – Active/Placebo</td><td colspan="5">19/19</td></tr>
<tr><td>Lipoma/Nodule size – diameter (cm)</td><td>1-1.9</td><td>2-3.9</td><td>4-5.9</td><td>6-7.9</td><td>8-10</td></tr>
<tr><td>Total Dose of RZL-012 in the RZL group (mg)</td><td>10</td><td>20</td><td>40</td><td>50</td><td>60</td></tr>
<tr><td>Number of Injections</td><td>2</td><td>4</td><td>8</td><td>10</td><td>12</td></tr>
</table>

The maximal total RZL-012 dose will be 240 mg per subject (a total of 48 injections at 5mg/injection; 33% higher than the highest dose that was tested on humans and 100% the No Observed Adverse Effect level [NOAEL].
The injections will be spread randomly on the lipoma surface with a distance between injections of at least 1 cm. Injections will be given at 90° to the injected skin surface.</td></tr>
</table>

	 Extension Phase: Placebo-treated subjects will be offered the option of receiving treatment with RZL-012 on a single occasion. Dosing will be calculated according to lipoma size (diameter) as determined by ultrasound and will follow the treatment regimen shown in the table above.
Visit Schedule	Subject site visits will be performed ± 1 day from scheduled date for Day 28 and Day 56 visit and ±2 days from scheduled date for Day 84 visit. All data relevant for the visits should be obtained within 3 days (e.g., blood test results) of visit. **Screening Day visit (Day -14 through -1):** - Following signing of the informed consent - assessment of subject eligibility will include: medical history, physical examination, vital signs, women in fertile age will be asked for pregnancy test, ECG, serology assays (HBV, HCV and HIV), clinical laboratory tests. - Ultrasound assessing lipoma/nodules size (diameter) and quality to determine which lipomas/nodules are to be injected with a total dose of up to 240 mg RZL-012. - Photography of injection site areas. Clinical laboratory tests will include: 1. Hematology: Complete blood count (CBC) including White blood cell [WBC] differential values, D-dimer, Fibrinogen and coagulation (International normalized ratio [INR], Partial thromboplastin time [PTT] and Prothrombin time [PT]). 2. Serum chemistry will include: Albumin, Albumin/Globulin Ratio (calculated), Alkaline Phosphatase, ALT, AST, BUN/Creatinine Ratio (calculated), Calcium, Carbon Dioxide, Chloride, Creatinine with GFR Estimated, Globulin (calculated), Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen. In addition, Amylase, Lactate dehydrogenase [LDH], Creatine-kinase MM [CK-MB], Creatine phosphokinase [CPK], Gamma-glutamyl transferase [GGT], Alkaline phosphatase [ALP]) and C-reactive protein [CRP] will be tested. 3. Lipid profile: Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Triglycerides (TG) and Fasting glucose. 4. Urinalysis: Protein, Red blood cells (RBC), WBC, Blood, Glucose, Ketone bodies, Bilirubin, Urine specific gravity, pH. **Baseline visit (Day 0):** - Pre-treatment: eligibility confirmation, vital signs, pregnancy test women, Draize score, clinical evaluation of local pain and tenderness to pressure (pain assessment) and lipoma/ nodules size assessment by ultrasound*, photography, QOL questionnaire

- Treatment - All injections will be administered 90° to the injected 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: vital signs (2h ± 30 min post injection). evaluation of skin irritancy by Draize score (2h post injection ± 30 min), adverse events (AEs) will be recorded.
  *In case of screening visit that will be conducted only one day before Baseline, ultrasound and photographs at Baseline visit are optional. The ultrasound parameters collected at screening will be used at Baseline visit.

Schedule visits (Day 1-56):

- Day 1 following treatment will include: ECG, vital signs including pulse rate, Draize score, clinical laboratory tests, urinalysis, lipid profile, AEs record. Subjects will start applying an anti-histamine gel.
- Day 7± 1d from treatment: Phone call for follow up.
- Day 28± 2d from treatment: ECG, physical exam, vital signs, clinical laboratory tests, urinalysis, Draize score, lipoma/nodule size assessment by ultrasound, clinical evaluation of local pain and tenderness to pressure, photographs, AEs record
- Day 56± 2d from treatment: physical examination, vital signs, Draize score, lipoma/nodule size assessment by ultrasound, clinical evaluation of local pain and tenderness to pressure, photographs, AEs record.
- Day 84± 2d from treatment:
  Draize score, photographs, assessment of lipomas/nodules size using US, clinical evaluation of local pain and tenderness to pressure, QOL questionnaire, AEs record.

In case a specific subject demonstrates elevated levels in one or more of the tested parameters, this subject will be followed up on day 56 to confirm return to normal levels.

<u>Open Label Extension Phase:</u>

Following the opening of the randomization codes, placebo subjects will be offered the option of receiving treatment with RZL-012. Subjects who choose this will be followed up for an additional 84 days for efficacy and safety as described below:

The physician will set up a date for injection with RZL-012 within 30 days of codes opening. This will be the baseline visit, Day 0. The following procedures will take place on Day 0 visit:

Day 0- Physical exam, Clinical laboratory tests (hematology, chemistry) lipid profile and urinalysis, ECG, injection with RZL-012, concomitant medication, vital signs – before and after the injection, ultrasound measurement of the lipomas, photography of the lipomas, QOL questionnaire, Draize score – before and after injection, pain score and AEs documentation.

Following RZL-012 injection, subjects will have the following visits:

Day 1 – ECG, vital signs, Draize score, clinical laboratory tests including urinalysis and lipid profile, AEs record.

Day 7 – Phone call visit. The study coordinator/nurse will call the subjects to ask about adverse events and general health.

Day 28±2 – ECG, physical exam, vital signs, clinical laboratory tests, urinalysis, Draize score, ultrasound measurement of the lipomas, photography of the lipomas, pain score and AEs documentation.

Day 56±2 - Physical exam, vital signs, ultrasound measurement of the lipomas, photography of the lipomas, Draize score, pain score and AEs documentation.

Day 84±2 - Ultrasound measurement of the lipomas, photography of the lipomas, QOL questionnaire, Draize score pain score, QOL questionnaire and AEs documentation.

Study Endpoints	**Placebo – Controlled Phase** **Primary Endpoint**: Average percent reduction in lipoma/nodule height on day 84 after injection vs baseline- evaluated by ultrasound in the RZL treatment group compared to the placebo group. **Key secondary Endpoint**: Reduction in local pain score per lipoma/nodule on Day 84 vs baseline as measured by the comparative Pain Scale **Other secondary endpoints:** 1. Evaluation of RZL-012 injection safety and tolerability in DD subjects. 2. Ultrasound evaluated percent lipomas/nodules with height reduction of at least 75% on Day 84 vs baseline in the RZL treatment group compared to the placebo group **Exploratory Endpoint** 3. Improvement in Quality of Life – QOL questionnaire **<u>Open Label Extension Phase:</u>** Primary end point: Average percent reduction in lipoma/nodule height on day 84 after injection vs baseline Secondary end points: 1. Reduction in local pain score per lipoma/nodule on Day 84 vs baseline as measured by comparative pain scale. 2. Evaluation of RZL-012 injection safety and tolerability 3. Improvement in Quality of life – QOL questionnaire
Sample Size	This study is a Phase 2b trial. A total of 38 evaluable DD subjects from 3-4 centers will be included in the study (19 will be injected with RZL-012 and 19 will receive placebo). Subjects will be followed up for 84 days after injection. Once the study ends and codes are opened, the 19 placebo-treated subjects will be offered the option of receiving treatment with RZL-012. Subjects who choose this will be followed up for an additional 84 days. The statistical considerations described below relate to the placebo-controlled phase of the study. **Based on primary endpoint:** Subjects will be randomized into two groups in a 1:1 ratio. The rationale for sample size calculation was based on data from Raziel's open label phase 2a study (Study #RZL-012-FD-P2aUS-001) in which a reduction in lipoma/nodule height of about 55% was demonstrated in the treatment group. This phase 2a study did not include a placebo group but studies reported by other groups show an average reduction from baseline in lipoma/nodule height of about 7% in the placebo group. Taking these numbers into consideration an effect size of 0.96 is expected (effect size = expected effect size in treated (0.55) – expected effects size in placebo group (0.07)/expected standard deviation (0.5)). Sample size justification: A sample size of 19 in each group (total sample size of 38) will have 80% power to detect a difference in means of 48 (the difference between a Group 1 mean, μ_1, of 55 and a Group 2 mean, μ_2, of 7) assuming that the common standard deviation is 50 using a two-group t-test with a 0.05 two-sided significance level. **Based on key secondary endpoint:** Subjects will be randomized into two groups with a 1:1 ratio. The rationale for sample size calculation was based on data from our open label phase 2a study (Study #RZL-012-FD-P2aUS-001) in which reduction in lipoma/nodule pain score of about 76% was demonstrated in the treatment group. Our phase 2a study did not include a placebo group but pain studies reported by other groups, show a range of reduction in pain score from +10% - -60% in the

	placebo group. Based on Geography, study size and length we selected an expected reduction from baseline of 25% in lipoma pain in our placebo group. Taking these numbers into consideration we expect an effect size of 1.02 (effect size = expected effect size in treated (0.76) – expected effects size in placebo group (0.25)/expected standard deviation (0.5)). Sample size justification: A sample size of about 19 in each group (total sample size of 38) will have 80% power to detect a difference in means of 51 (the difference between a Group 1 mean, μ_1, of 76 and a Group 2 mean, μ_2, of 25) assuming that the common standard deviation is 50 using a two-group t-test with a 0.05 two-sided significance level.
Statistical Methods	**Descriptive Statistics:** All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For categorical variables summary tables will be provided giving sample size, absolute and relative frequency and 95% CI (Confidence Interval) for proportions by study group. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum and 95% CI (Confidence Interval) for means of variables by study group. All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant. The data will be analyzed using the SAS ® version 9.4 (SAS Institute, Cary North Carolina). **Analysis of Efficacy for Primary Endpoint** • **Analysis per patient (based on 4-8 lipomas/nodules per patient)** The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule height at day 84 after injection vs. baseline. Analysis of covariance (ANCOVA) model will be applied in order to identify covariate parameters suspected as related to reduction in lipoma/nodule height and in order to test the differences in percent reduction of lipoma/nodules height between the treatment groups adjusted to the above covariates. • **Analysis per lipoma/nodule (based on 4-8 lipomas/nodules per patient)** The MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference between the groups in percent reduction of lipoma/nodule height from baseline to day 84, and adjusted for the above covariates as appropriate **Analysis of Efficacy for key secondary Endpoint** • **Analysis per patient (based on 4-8 lipomas/nodules per patient)** The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule pain at day 84 after injection vs. baseline. Analysis of covariance (ANCOVA) model will be applied in order to identify covariate parameters suspected as related to reduction in lipoma/nodule pain and in order to test the differences in percent reduction of lipoma/nodules pain between the treatment groups adjusted to the above covariates. • **Analysis per lipoma/nodule (based on 4-8 lipomas/nodules per patient)** The MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference between the groups in percent reduction in local pain score at day 84 vs. baseline between the study groups adjusted for the above covariates as appropriate.

	Analysis of other Secondary Endpoints **1. Analysis of Safety** Safety data from the study will be summarized descriptively by treatment. The incidence of AEs will be presented by treatment. 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. Draize scores will be presented in tabular format by visit and treatment. Serious adverse events (SAEs) will be described in narratives as part of the study report. **2. Analysis of Efficacy** Clearance of nodules: (Analysis per Lipoma based on 4-8 lipomas per patient): 95% Confidence Interval (CI) will be calculated for the proportion of responding nodules (response will be defined as achieving a reduction in lipoma height of at least 75% vs. baseline) by study groups. GEE (Generalized Estimating Equations) model will be applied for testing the statistical significance of the difference in percent of responding nodules (nodules with at least 75% clearance at day 84 vs. baseline) between the study groups, with adjustment to suspected confounders.
Study Duration	Study duration for each patient will be 3.5 months, including enrollment, treatment and follow-up period. Each subject will participate in the study for up to 98 days as part of this protocol. Placebo subjects who continue to the open label extension part may participate for an additional 84 days.
Study Sites	4

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. Scientific Background and Clinical Rationale

Dercum's disease (DD) was first described in 1888 by American neurologist Francis Xavier Dercum. It is a rare adipose disorder (RAD) and is typically characterized by obesity and chronic pain (> 3 months) in the subcutaneous adipose tissue (SAT). The pain associated with DD is often debilitating and resistant to typical analgesic treatments. In addition, there are a large number of associated symptoms such as fatty deposits (lipomas), easy bruising, sleep disturbances, impaired memory, depression, difficulty concentrating, anxiety, rapid heartbeat, shortness of breath, diabetes, bloating, constipation, fatigue, and joint pain (1).

DD can be classified into 4 types which include: generalized diffuse, generalized nodular, localized nodular, and juxta-articular forms. The diffuse type is characterized by widespread pain from SATs located anywhere from the head to the soles of the feet, without any clear lipomas. Generalized nodular typically occurs with widespread, painful adipose tissue that is more painful in the vicinity of lipomas, whereas in the localized nodular type, the pain is confined to areas within and around lipomas. Finally, the juxta-articular type is characterized by painful folds or nodular fat around joints such as the knees and/or the hips (2). There are Dercum's subjects who have mixed lipomas, i.e. small and large lipomas.

The etiology of DD is currently unknown. Several hypotheses have been proposed including nervous system dysfunction (3), adipose tissue dysfunction (4), lymphovascular disorder, endocrine dysfunction, mechanical pressure on nerves, and a result of trauma (5). Interestingly, there are a few reports that suggest that DD can be an inherited autosomal dominant disorder with variable expression, however the majority of cases occur sporadically without any specific genetic mutations (2).

The actual prevalence of DD in the USA and around the world has not yet been established. The disease mostly appears between the ages of 35 and 50 years and is six times more common in women than in men (6,7). Recently, an estimation of 3 Key Opinion Leaders (KOLs) in the US, estimated that the prevalence of the disease varies between 1,500–115,000 people (8-10).

No specific treatment exists for DD. Treatment is mainly symptomatic and supportive and is primarily focused on easing the characteristic painful episodes. Various analgesics have been tried with limited effectiveness (i.e., lidocaine) (11,12). Surgical excision of lipomas may temporarily relieve symptoms although recurrences often develop. Liposuction has been used as a supportive treatment for some individuals with DD and may provide an initial reduction in pain and improvement in quality of life (QOL) (13,14). 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.

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

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

In the initial exploratory clinical trial that was conducted (RZL-012-P0US-001.3 under IND 119941) to test safety and thermogenesis-induction of RZL-012 in overweight and obese subjects, RZL-012 was found to be safe with mainly transient and local adverse events (AEs). A thermogenic effect (a rise of 1 °C in temperature at the injected site compared to the untreated collateral side) was evident in the RZL-012-treated subjects of the highest dose cohort (20 mg/subject). Moreover, MRI at 28 days after injection demonstrated that fat mass was reduced at the injection site compared to matched fat mass at the non-injected contralateral site, in RZL-012 but not in vehicle-treated subjects.

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

An additional Phase 2a study (RZL-012-FD-P2aUS-001.7 under IND 135762) was conducted to evaluate the safety and pharmacodynamic response to RZL-012 in lipedema and DD subjects. Five (5) DD subjects had a 55% reduction in height of 18 injected lipomas. In addition, a significant reduction in lipoma pain was noted. Safety and tolerability were good. The Adverse Events (AEs) that were categorized as definitely related to the study drug were transient and localized to the injection site.

Based on the above, Raziel concludes that the safety profile of RZL-012 is good and acceptable and the compound is efficacious in long-term reduction of local subcutaneous fat mass (SFM). Thus, Raziel-012 will be further tested in a larger population of DD subjects and its efficacy will be compared to placebo treatment in a double-blind placebo-controlled trial.

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 (250 mg RZL/5 mL vial = 50 mg RZL/mL), was manufactured and packaged 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 clinical Good Manufacturing Practices (cGMPs).

1.2. CLINICAL STUDIES CONDUCTED BY RAZIEL

RZL-012 has been tested in 3 clinical trials, having a total of 54 exposed subjects at single doses of up to 180 mg/subject. Table 1 describes the clinical trials conducted by Raziel Therapeutics.

Table 1: Summary of Clinical Trials Conducted by Raziel Therapeutics

Study ID STATUS	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population
RZL-012-P0US-001.3 **COMPLETED**	0	USA	Phase 0 Study for evaluation of safety and thermogenesis in Overweight Healthy Volunteers injected with 3 escalating Doses of RZL-012	A randomized, double-blind, vehicle-controlled, dose-escalation study with 8 subjects/cohort, (6 active and 2 controls)	Cohort 1: 5 mg Cohort 2: 10 mg Cohort 3: 20 mg	Healthy, 20-40 year old, overweight by Body Mass Index (BMI) definition (25 < BMI ≤ 34.9), adult males.
RZL-012-P2aUS-001.4 **COMPLETED**	2A (obese)	USA	A Double Blind, Randomized, Placebo Controlled, Dose Escalation Phase 2a Clinical Trial for the Evaluation of Safety and Thermogenesis-induction of RZL-012 in Overweight and Obese Volunteers	A randomized, double-blind, placebo-controlled, consecutive 4 cohort, dose escalation clinical trial	Cohort 1: 40 mg Cohort 2: 80 mg Cohort 3: 120 mg Cohort 4: 180 mg	Adult male subjects 20–60 years old, with 27.5 < BMI ≤ 34.9

Study ID STATUS	Phase	Country	Study Title	Study Design	Dosing Regimen	Study Population
RZL-012-FD-P2aUS-001 **COMPLETED**	2A (DD and lipedema)	USA	An Open Label, Phase 2a Clinical Trial for the Evaluation of Safety and Efficacy of RZL-012 for the Treatment of Women with Lipedema Involving Substantial Fat above the Knee or of Women and Men with Nodular Dercum's Disease	Open-label safety and efficacy clinical trial	Cohort 1 DD: up to 40 mg RZL-012 per subject in 6 subjects Cohort 2 Lipedema: up to 80 mg RZL-012 per subject in 6 subjects	DD : men 20–65 years old and post-menopausal (at least 2 years) women <65 years old with nodular Dercum's disease Lipedema : post-menopausal (at least 2 years) women <65 years old with lipedema involving substantial fat above the knee

1.2.1. Overall Safety Summary:

The majority of adverse events (AE)s after RZL-012 injection were related to local injection site reactions. There was no correlation between RZL-012 dose increase and severity or duration of local reaction. Most injection site reactions were transient and were not observed for more than 28 days following injection. There were no significant changes in blood parameter values except for 2 cases as reported in the 2 studies indicated for obesity. In study RZL-012-P0US-01.3 (Phase 0) there was one subject injected with 20 mg of RZL-012 who demonstrated a significant increase in liver enzymes. However, when these parameters were reviewed carefully among other subjects injected with higher doses of RZL-012 (up to 9 times i.e., 180 mg), this phenomenon was not repeated. In preclinical studies which were conducted by Raziel, a rise in aspartate aminotransferase (AST) enzyme levels was observed at high doses in female rats (20 mg/rat equivalent to a human dose >>500 mg/subject), getting back to normal levels within 14 days following injection. The relationship between RZL-012 injection and increased levels of liver enzymes in this subject is not completely understood. Raziel Therapeutics continues to monitor closely for any changes in liver enzymes.

The second case was reported in RZL-012-P2aUS-01.4 study (Phase 2a in obese subjects). Subjects which were injected with the maximal dose of 180 mg had an average 3-fold increase of D-dimer values at Day 3 compared to Day -1. However, levels went down by Day 7.

1.2.2. Efficacy summary:

Measurements of lipoma size in 6 DD subjects who participated in study RZL-012-FD-P2aUS-001, included ultrasound measurements of height, width and length for 21 injected lipomas. Each subject was dosed up to 40mg of RZL-012 that was injected into several lipomas. The mean reduction in lipomas height on day 56 after injection vs. baseline was 47.9±44.1% ($P<0.001$).

Lipoma pain was measured by the comparative pain scale in 19 of 21 injected lipomas in 6 DD pts (specific pain assessment per each lipoma). The mean reduction in lipoma pain on day 56 after injection vs. baseline was 70.7±36.9% (P<0.0001).

Further details are provided in the IB.

The current clinical trial in DD subjects will have a single injection session of RZL-012 at doses up to 240 mg/subject, (up to 48 injections) and will be the first trial to assess efficacy of RZL-012 vs. placebo in DD subjects.

2. PURPOSE AND STUDY OBJECTIVES

2.1. PURPOSE

This is a double blind, randomized, multi-center, placebo controlled 2b clinical trial for the evaluation of efficacy and safety of RZL-012 in women or men having DD lipomas.

2.2. STUDY OBJECTIVES

The primary and secondary endpoints described below relates to the placebo-controlled study.

2.2.1. Primary

To evaluate the average percent reduction in lipoma/nodule height on day 84 after injection vs baseline- evaluated by ultrasound in the RZL treatment group compared to the placebo group.

2.2.2. Secondary

The secondary objectives are to evaluate the efficacy and safety of RZL-012 subcutaneous injections in the lipomas vs. placebo by:

- Evaluating the reduction in local pain score per lipoma/nodule on Day 84 vs baseline as measured by the comparative pain scale. This secondary endpoint will be a key endpoint.
- Evaluating safety and tolerability of RZL-012 injection in DD subjects.
- Evaluating percent lipomas/nodules with height reduction of at least 75% on Day 84 vs baseline as measured by ultrasound.

2.2.3. Exploratory

- Improvement in Quality of Life – using a QOL questionnaire

2.3. DESCRIPTION OF STUDY DESIGN

This is a multi-center, randomized, double blind, placebo controlled clinical trial in DD subjects having lipomas. Subjects will be randomized, in a 1:1 ratio, into two groups injected with either RZL-012 or vehicle.

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

At least 4 lipomas/nodules, preferably 6, and no more than 8, will be injected per subject. Dosing will be according to lipoma size, where the total injected dose will not exceed 240 mg per patient (48 injections at 5mg/injection).

2.4. DOSE RATIONALE

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

In the current trial, a maximal dose of up to 240 mg (33% higher than the maximal dose tested in humans) will be injected per subject. This will allow injection of the desired number of lipomas per patient (4-8 lipomas).

The dosage of RZL-012 per each lipoma was set according to its size (diameter), as determined by ultrasound, and is higher than dosage per lipoma in the previous study. This alteration was made to enhance efficacy of RZL-012. Injections will be comprised of 5 mg each, and will be spread randomly on lipoma surface with a distance between injections of at least 1 cm. A distance of 1 cm will allow a good distribution RZL-012 into lipoma fat.

2.5. DOSING

2.5.1. Dosing Regimen

All subjects will receive a single treatment of RZL-012 or placebo in multiple injection sites according to lipomas size, as shown in Table 2 below.

All subjects assigned to the RZL-012 treatment group will be dosed at a maximal dose of 240 mg RZL-012. Dosing will be calculated according to lipoma size (diameter) as determined by ultrasound in a dose of 5mg per in a volume of 0.1ml. Placebo treated subjects will be dosed with the same vehicle volume as calculated for the RZL-012 group.

Table 2: Study Design

Number of Subjects – Active/Placebo	19/19				
Dose of RZL-012(mg)/vehicle (mL) per single injection	5mg/0.1mL				
Lipoma/Nodule size – diameter (cm)	1-1.9	2-3.9	4-5.9	6-7.9	8-10
Total Dose of RZL-012 in the RZL group (mg)	10	20	40	50	60
Number of Injections	2	4	8	10	12

Injections will be given perpendicular (90°) to injected skin surface and will be spread randomly, at least 1cm apart.

Dosing of subjects in Open Label Extension Phase:
Dosing will be calculated according to lipoma size (diameter) as determined by ultrasound and will follow the treatment regimen as shown in Table 2.

3. STUDY ENDPOINTS

The primary and secondary endpoints described below relates to the placebo-controlled phase of the study:

3.1. PRIMARY ENDPOINTS

The primary endpoint for this trial is the average percent reduction in lipoma/nodule height on day 84 after injection vs baseline, in the RZL treated group as compared to the placebo treated group. Lipoma height will be assessed by ultrasound.

A total of 38 subjects will be randomized to receive active treatment or placebo (1:1) at 4 clinical sites. Subjects will be dosed according to size/diameter of selected lipomas with a dose of up to 240 mg RZL-012/patient in the RZL-012 group or up to 4.8mL vehicle/patient in the placebo group.

3.2. KEY SECONDARY ENDPOINT:

The key secondary endpoint for this trial is the average percent reduction in lipoma/nodule pain on day 84 after injection vs baseline, in the RZL-treated group as compared to the placebo-treated group. Lipoma pain will be assessed by the Comparative Pain Scale.

3.3. OTHER SECONDARY ENDPOINTS

1. Safety and tolerability of RZL-012 dosing to DD subjects vs. placebo dosed subjects.

2. Percent responding lipomas/nodules (a responding lipoma is defined as having more than 75% height reduction on day 84 after injection vs baseline), in the RZL treated group as compared to the placebo treated group.

3.4. EXPLORATORY END POINTS

Assessment of Improvement in Quality of Life using QOL questionnaire following treatment.

3.5. OPEN LABEL EXTENSION PHASE ENDPOINTS:

3.5.1. Primary end point:

Average percent reduction in lipoma/nodule height on day 84 after injection vs baseline

3.5.2. Secondary end points:

1. Reduction in local pain score per lipoma/nodule on Day 84 vs baseline as measured by comparative pain scale.

2. Evaluation of RZL-012 injection safety and tolerability

3. Improvement in Quality of life – QOL questionnaire

4. STUDY POPULATION

4.1. INCLUSION CRITERIA

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

1. Women and men, 18- 70 years old.
2. At least 4 painful lipomas of appropriate size to be injected on a background of DD.
3. Generally considered healthy according to medical history, physical examination, electrocardiogram (ECG) and laboratory evaluation with an emphasis on metabolic parameters (fasting glucose concentration < 200 mg/dL).

4. Subjects must be able to adhere to the visit schedule and protocol requirements and be capable of completing the study.
5. Males or females in the age of fertility are willing to refrain from sexual activity or agree to use a double-barrier contraceptive device (e.g., condom and spermicide) for 4 weeks after treatment with RZL-012.
6. Subjects must sign an informed consent indicating they are aware of the investigational nature of the study.

4.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded:

1. Unable to tolerate subcutaneous injections.
2. Pregnant women.
3. Subjects with uncontrolled cardiac, hepatic, renal or neurologic/psychiatric disorders, that in the opinion of the investigator places the subject at significant risk.
4. Positive blood screen for Hepatitis B surface antigen (HbSAg), Hepatitis C virus (HCV), or Human immunodeficiency virus (HIV).
5. Subjects with a clinical history of active primary or secondary immunodeficiency, autoimmune disease or subjects taking immunosuppressive drugs such as corticosteroids.
6. Subjects with dysfunctional gallbladder activity, e.g. underwent cholecystectomy or cholecystitis.
7. As a result of medical review and physical examination, the PI (or medically qualified nominee) considers the subject unfit for the study.
8. Known sensitivity to components of the injection formulation.
9. Prior wound, tattoo or infection in the treated area.
10. Prior invasive treatment such as surgery or injectable drug at the RZL-012 injected area.
11. Subjects treated chronically at least 3 months prior to study entry with systemic steroids or immunosuppressive drugs.
12. Subjects treated chronically at least one week prior to study entry with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).
13. Current participation or participation within 3 months prior to the start of this study in a drug or other investigational research study.

4.3. SUBJECT IDENTIFICATION

At each site, a unique code number 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 will be used in lieu of the subject's name when the investigator reports AEs and/or other trial related data.

4.4. REMOVAL, REPLACEMENT OR EARLY WITHDRAWAL OF STUDY SUBJECTS

Study subjects withdrawing prior to injection (withdrawal between screening and baseline visits) will be replaced. Subjects withdrawing after injection on baseline visit will not be replaced and will be followed up as possible. Subjects experiencing serious side effects will be withdrawn from the study and followed up until the event resolves or becomes stable.

5. STUDY PROCEDURES AND ASSESSMENT

5.1. DEFINITIONS OF STUDY PROCEDURES

5.1.1. 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/she 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.

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.

5.1.2. Medical History

Subjects' medical history should be fully documented at Screening Day (14 through 1 day prior to baseline), to ensure compliance with study inclusion criteria and the absence of circumstance mentioned in the exclusion criteria. Medical history information must include, but not be limited

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

5.1.3. 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.

5.1.4. Physical Examination

The investigator (or medically qualified nominee) will conduct a complete physical examination, height and weight measurements at Screening Day (performed 14 through 1 day 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 will be performed on study visit on Day 28 and 56 following treatment.

5.1.5. Pain Measurement

Local lipoma pain, as determined by the Comparative Pain Scale, will be measured at Baseline visit prior to injection, in order to establish a baseline for comparison following drug injection. Subjects will complete a comparative pain scale score for each lipoma selected for injection.

Additional pain measurements for the treated lipomas will be performed on study visit Days 28, 56, and 84 after injection.

A description of the comparative pain sale is presented in Appendix II.

5.1.6. Quality of Life Assessment

QOL will be measured in subjects at Baseline visit in order to establish a baseline for comparison after drug injection. For this purpose, the Short Form 36 questionnaire (See Appendix III) will be used to evaluate the improvement in the QOL of active vs. placebo group subjects.

Additional assessment of QOL will be performed on the Day 84 visit.

5.1.7. Vital Signs Measurements

Subjects' vital signs will be measured at Screening Day (performed 14 through 1 day 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 on 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 Day 28 and Day 56 following injection.

5.1.8. Serology assay

Assays for Hepatitis C virus (HCV), Hepatitis B Surface Antigen (HbSAg), and human immunodeficiency virus (HIV) will be conducted on Screening Day 1 (performed 14 through 1 day prior to baseline) in order to ensure compliance with study inclusion criteria.

5.1.9. Clinical Laboratory tests

Clinical laboratory tests will be conducted on Screening Day (performed 14 through 1 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 for each set of tests. 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 8.

5.1.9.1. Hematology

Hematology tests will be conducted at Screening Day (performed 14 through 1 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 study visit Day 1 and Day 28 following injection.

Hematology tests will include Complete blood count (CBC) including White blood cell (WBC) differential values, D-dimer, Fibrinogen and coagulation (International normalized ratio (INR), Partial thromboplastin time (PTT) and Prothrombin time (PT)).

In case a specific subject demonstrates elevated blood levels in one or more of the tested parameters, this subject will be followed up on day 56 to confirm return to normal levels.

5.1.9.2. Serum Chemistry Analysis

Testing of blood chemistry values will be conducted on Screening Day (performed 14 through 1 days prior to baseline) in order to ensure compliance with study inclusion criteria.

Additional Serum Chemistry testing will be conducted on Day 0 (before injection), 24hr ± 2hr following injection and on study visit Day 1 and Day 28 following injection.

Serum chemistry will include:

Albumin, Albumin/Globulin Ratio (calculated), Alkaline Phosphatase, ALT, AST, BUN/Creatinine Ratio (calculated), Calcium, Carbon Dioxide, Chloride, Creatinine with GFR Estimated, Globulin (calculated), Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen. In addition, Amylase, Lactate dehydrogenase [LDH], Creatine-kinase MM [CK-MB], Creatine phosphokinase [CPK], Gamma-glutamyl transferase [GGT], Alkaline phosphatase [ALP]) and C-reactive protein [CRP] will be tested.

In case a specific subject demonstrates elevated blood levels in one or more of the tested parameters, this subject will be followed up on day 56 to confirm return to normal levels.

5.1.9.3. Urinalysis

Urinalysis will be conducted at Screening Day (performed 14 through 1 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 1 and 28 following injection.

Urinalysis will include: Protein, Red blood cells (RBC), WBC, Blood, Glucose, Ketone bodies, Bilirubin, Urine specific gravity and pH.

In case a specific subject demonstrates elevated blood levels in one or more of the tested parameters, this subject will be followed up on day 56 to confirm return to normal levels.

5.1.9.4. Lipid profile

Lipid profile will be conducted on Screening Day (performed 14 through 1 days prior to baseline) in order to allow differential diagnosis in case of lipid circulation in blood following injection.

Additional lipid profile testing will be conducted on Day 1 visit following injection.

Lipid profile will include: Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Triglycerides (TG) and Fasting glucose.

5.1.10. ECG

Subjects' ECG will be performed on Screening Day (performed 14 through 1 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 Day 1 and Day 28 visits following injection.

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.

5.1.11. Draize Score

Subjects' skin irritancy will be evaluated by Draize score. Draize score will be assessed for each selected lipoma for injection before treatment in order to establish a baseline for comparison following drug injection.
Additional skin irritancy evaluation to assess skin condition will be performed on baseline visit 2h ± 30min following injection and on study visits Day 1, 28, 56 and 84 following injection. Skin irritancy observations at the injected 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

5.1.12. Photography of lipomas

Documentation of the lipoma location and its skin condition in the injected area will be conducted at Screening Day (performed 14 through 1 days prior to baseline). Additional photography will be performed at Baseline visit pre injection, Day 28, Day 56 and Day 84 visit.

Photography with a digital camera will include:

a. A picture from above – will be taken perpendicular to lipoma top at a minimum distance of 5 cm or less and the distance noted and repeated throughout the study
b. A side picture – will be taken parallel to lipoma to at a minimum distance of 5 cm or less and the distance noted and repeated throughout the study.

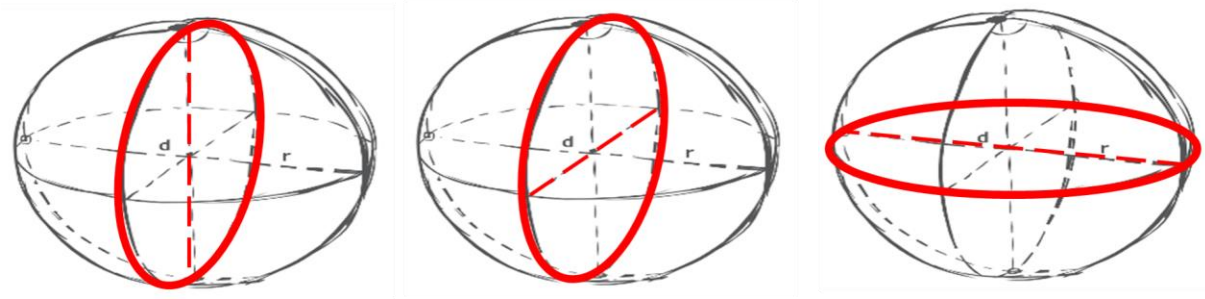
5.1.13. Imaging: Ultrasound (US)

Evaluation of Ultrasound will be conducted at Screening (performed 14 through 1 days prior to baseline) to ensure compliance with study inclusion criteria and establishing a baseline. Nodule size and tissue characteristics will be documented. Additional US will be performed on Day 0. In case of screening visit that will be conducted only one day before Baseline, ultrasound and photographs at Baseline visit are optional. The ultrasound parameters and phots collected at screening will be used at Baseline visit. In case the study personnel decide to inject different lipomas than those that were chosen at the screening visit, then ultrasound evaluation is mandatory on Day 0 . Additional US measurements for the injected lipomas will be done at Days 28, 56 and 84 visits and the change in dimensions will be compared to the recorded dimensions at baseline.

Ultrasound imaging will be conducted on Day 0 (before injection) in order to ensure proper dose injection according to measured nodule size/diameter. In case of screening visit that will be conducted only one day before Baseline, ultrasound and photographs at Baseline visit are optional. The ultrasound parameters collected at screening will be used at Baseline 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**

5.1.14. Adverse Events

The information obtained during periodic subject 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.

Thirty-eight (38) subjects (19 active and 19 placebo) will be injected with a dose of up to 240 mg/subject in the RZL-012 group or with up to 4.8 mL of vehicle in the placebo group.

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 84 days after injection.

5.1.15. Evaluation of Response

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

5.1.15.1. Evaluation of Primary Endpoints

5.1.15.1.1. Ultrasound to assess lipoma/nodule dimension after treatment

Local fat reduction will be evaluated by ultrasound. Local fat reduction is defined as the reduction in nodule height at the injected area as compared to baseline and as a function of treatment (active/placebo). Ultrasound of the injected lipomas/nodules will be conducted at baseline and on Days 28, 56 and 84 following treatment.

5.1.15.2. Evaluation of Secondary Endpoints

5.1.15.2.1. Pain – A key secondary endpoint

Improvement in local pain will be assessed by pain scoring of each lipoma/nodule on study Days 28, 56 and 84 following injection and comparing to baseline assessments. This evaluation will be done using the comparative pain scale.

5.1.15.2.2. Safety monitoring

Safety and tolerability will be assessed, according to definitions and guidelines, by the medical staff (e.g., PI, site coordinator, and study nurse) and the study subjects:

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. Lipid profile.
6. ECG.

Subjects questioning - full medical history during screening, routine AE reporting and tolerability monitoring.

5.1.15.3. Exploratory endpoints

5.1.15.3.1. Improvement in QOL

QOL of RZL-012 treated vs. placebo subjects will be assessed 84 Days vs. baseline visit in order to compare whether there is an improvement in subject's QOL as a function of treatment.

5.1.15.4. 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.

5.1.15.5. 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).

5.1.15.6. 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.

5.2. 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.

5.2.1. 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 14 days ahead and no later than 1 day prior to baseline visit.

Study Screening Day procedures will include the following:

- Informed Consent - Section 5.1.1
- Medical History - Section 5.1.2
- Concomitant Medication - Section 5.1.3
- Physical Examination - Section 5.1.4
- Vital signs Measurement –Section 5.1.7
- ECG – Section 5.1.10
- Serology – 5.1.8
- Clinical laboratory tests – Section **Error! Reference source not found.**
- Photography of injected lipomas – Section **Error! Reference source not found.**
- Ultrasound to measure lipoma/nodule dimensions - Section 5.1.13

Subjects may be rescreened if they were screened and did not completed their blood and urine tests 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.

5.2.2. Study Randomization

Subjects will be randomized to each study group, i.e., investigational therapy or control, according to a predefined randomization scheme in a ratio of 1:1 (active:placebo) among the 4 clinical sites. The investigational therapy group will be treated with RZL-012 and the control group will be treated with the same formulation (vehicle) as with RZL-012, absent active medication.

Assignment to study group will be disclosed only after subject eligibility is confirmed and immediately before treatment initiation. The investigator and the clinical staff will be masked to the treatment. The subjects will also be blinded and will not know whether he or she is injected with active or placebo treatment.

5.2.3. Study Treatment

5.2.3.1. Treatment with RZL-012 Investigational Drug

RZL-012 or vehicle will be supplied as a single vial for a single treatment session per subject. Up to 48 injections will be dosed to 4-8 lipomas per each subject.

Overall dose, dosing regimen and injection technique is crucial for safety of study participants.

Syringes will be filled with the desired volume for injection of RZL-012 or vehicle. All injections will be administered at 90° to injected skin, 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. An attempt to pull the plunger should be made before injecting to ensure that no blood is coming out. If so, the plunger should be pushed down to inject the medicine. The formulation is viscous and therefore resistance is expected while injecting.

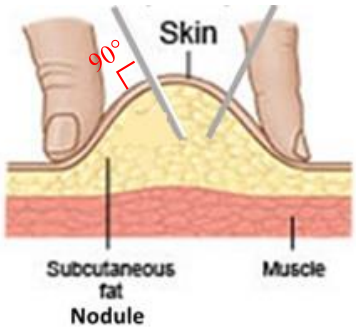
The injected volume will be calculated according to lipoma size (Table 3):

Table 3: Injected volume and dosages of RZL-012 / Placebo according to lipoma size

Number of Subjects – Active/Placebo	19/19				
Lipoma/Nodule size – diameter (cm)	1-1.9	2-3.9	4-5.9	6-7.9	8-10
Total Dose of RZL-012 in the RZL group (mg)	10	20	40	50	60
Number of Injections	2	4	8	10	12

Injections will be given perpendicular (90°) to injected skin surface towards the center of the nodule and the distance between injections in a nodule will be at least 1 cm (Figure 1). The dosing will be done in gradual injections of each 0.1mL into the tissue.

Figure 1: RZL-012/ Placebo Injection Sites in DD Subjects



Each RZL-012 kit contains 1 vial (250 mg/5 mL) enabling injection of the maximal dose per subject, 240mg. RZL-012 or vehicle will be injected on study Day 0 visit (baseline).

After completing injections of lipomas, an ice/cold pack will be applied onto the injection sites for immediate pain relief and will be held by the subject for at least 2 minutes. Following completion of injection procedures, subjects will remain in the clinic for an additional 2 hours ±30min for medical supervision and in order to follow adverse events after injection. During the stay in the clinic there are no restrictions in terms of activity or diet.

5.2.4. Treatment with Placebo

Nineteen (19) subjects randomly assigned to the study will be injected with placebo, which will be a vehicle control (tween-80, propylene glycol, benzyl alcohol and water) in the same manner as mentioned above (Section 5.2.3.1).

5.2.5. Baseline Visit

Baseline visit on day 0 will be performed to complete screening evaluation, and to review all procedures necessary to confirm subject eligibility prior to dosing. Subjects will stay under supervision in the study center for 2 hours ± 30 minutes following drug injection.

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

Table 4: Subject Information and Timeframes for the Placebo controlled Phase of the Study:

Information	Timeframe	Follow-up Timeframe
Informed Consent Form	Signed prior to any study dedicated procedure	
Medical History	At Screening Day visit	
RZL-012 dosing	At baseline (day 0)	
Concomitant Medications	At screening Day visit, Day 0, 1,7,28,56,84	
Physical examination	At Screening Day visit and at Days 28, 56	
Vital Signs	At Screening Day visit and at Days 0 (pre- and following injection), 1, 28, 56	
Pregnancy test (women only)	Will be performed at Baseline	
ECG	At screening, Day 1, 28	
Draize Score at the Injected Site	At Days 0 (pre- and following injection), 1, 28, 56	Day 84
Ultrasound for nodule size assessment	At Screening Day visit and at Days 0*, 28, 56	Day 84
Photography of the Injected Sites	At Screening Day visit and at Days 0*, 28, 56	Day 84
Pain assessment using Comparative Pain Scale	At Days 0, 28, 56	Day 84
QOL assessment	At day 0	Day 84
Serology assays (HbSAg, HCV and HIV)	At Screening Day visit	
Serum chemistry and Hematology	At Screening Day and at Days 1, 28	
Urinalysis	At Screening Day and at Days 1, 28	
Lipid Profile	At Screening Day and at Day 1	
AEs assessment	At Days 0, 1, 7, 28, 56	Day 84

* In case of screening visit that will be conducted only one day before Baseline, ultrasound at Baseline visit is optional. The ultrasound parameters and photography collected at screening will be used at Baseline visit.

Table 5: Subject Information and Timeframes for the Open Label Extension Phase:

Information	Timeframe	Follow-up Timeframe
RZL-012 dosing	At baseline (day 0)	
Concomitant Medications	At Day 0, 1,7,28,56,84	
Physical examination	At Day 0, 28, 56	

Information	Timeframe	Follow-up Timeframe
Vital Signs	At Days 0 (pre- and following injection), 1, 28, 56	
ECG	At Day 0, 1, 28	
Draize Score at the Injected Site	At Days 0 (pre- and following injection), 1, 28, 56	Day 84
Ultrasound for nodule size assessment	At Day 0 visit and at days 28, 56	Day 84
Photography of the Injected Sites	At Day 0 visit and at days 28, 56	Day 84
Pain assessment using Comparative Pain Scale	At Days 0, 28, 56	Day 84
QOL assessment	At day 0	Day 84
Serum chemistry and Hematology	At Day 0 and at Days 1, 28	
Urinalysis	At Day 0 and at Days 1, 28	
Lipid Profile	At Day 0 and at Day 1	
AEs assessment	At Days 0, 1, 7, 28, 56	Day 84

5.2.6. Subject Site Visits

Subject site visits will be performed ± 2 days from scheduled date (for study visit Days 28, 56 and 84). Day 7 phone call to the subject will be performed ±1 day from scheduled day.

For site visits that result in study discontinuation, see termination visit in Section 5.2.7.

5.2.7. Termination Visit

Once study is discontinued, all reasonable measures should be taken to perform a termination visit. Termination visit should include all procedures necessary to complete subjects' records: AE reporting, evaluation of response and updating of subject contact information. An effort should be made to perform all activities conducted on visit Day 84 for subjects who participates in the double-blind randomized placebo controlled study.

5.2.8. Unscheduled Visit

Unscheduled visits will be performed upon investigator's discretion, upon Sponsor request to redo tests with unusual results or complete missing results and may occur upon subject’s decision with no notification in advance. Unscheduled visits will include any study procedure deemed necessary, as described in Section 5.1.

6. DESCRIPTION OF THE OPEN LABEL EXTENSION PHASE OF THE STUDY

At study completion, the randomization codes will be opened. Nineteen (19) Subject who were injected with placebo will be offered to be treated with RZL-012.

At least 4 lipomas/nodules, preferably 6, and no more than 8, will be injected per subject. Dosing will be according to lipoma size, where the total injected dose will not exceed 240mg per patient (48 injections at 5mg/injection).

Dosing will be done according to lipoma size, as described in Table 6:

Table 6: Dosing of RZ-012 in the Open Label Extension Phase

Number of Subjects – Active/Placebo	19/19				
Lipoma/Nodule size – diameter (cm)	1-1.9	2-3.9	4-5.9	6-7.9	8-10
Total Dose of RZL-012 in the RZL group (mg)	10	20	40	50	60
Number of Injections	2	4	8	10	12

The injection with RZL-012 will be done within 30 days of randomization codes opening.

The day that will be set up by the physician for RZL-012 injection will be the baseline visit, Day 0.

On this day, each subject will have the procedures, as described in Section 5.1:

Day 0- Physical exam, Clinical laboratory tests (hematology, chemistry) lipid profile and urinalysis, ECG, injection with RZL-012, concomitant medication, vital signs – before and after the injection, ultrasound measurement of the lipomas*, photography of the lipomas, QOL questionnaire, Draize score – before and after injection, pain score and AEs documentation.

Day 1 – ECG, vital signs, Draize score, clinical laboratory tests including urinalysis and lipid profile, AEs record.

Day 7 – Phone call visit. The study coordinator/nurse will call the subjects to ask about adverse events and general health.

Day 28±2 – ECG, physical exam, vital signs, clinical laboratory tests, urinalysis, Draize score, ultrasound measurement of the lipomas, photography of the lipomas, pain score and AEs documentation.

Day 56±2 - Physical exam, vital signs, ultrasound measurement of the lipomas, photography of the lipomas, Draize score, pain score and AEs documentation.

Day 84±2 - Ultrasound measurement of the lipomas, photography of the lipomas, QOL questionnaire, Draize score pain score, QOL questionnaire and AEs documentation.

Schedule of events of the open label extension part is presented in Appendix 2.

7. SAFETY CONSIDERATIONS AND GUIDANCE FOR INVESTIGATORS

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

7.1. STUDY RESTRICTIONS REGARDING CONCOMITANT MEDICATIONS

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

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

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

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

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

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

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 and in previous clinical studies, as introduced in the ICF.

The AEs of RZL-012 vs. placebo will be evaluated for their frequency, severity and duration.

7.3. PREMATURE DISCONTINUATION FROM STUDY

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

- Subject's request.
- Any life-threatening AE.
- Systemic hypersensitivity reaction.
- Any serious or severe ADR (defined in Section 9.3) clinically evaluated by the PI and/or Sponsor as warranting subject discontinuation.
- Non-compliance: Subject's non-compliance with study procedures, 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 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 is an investigational drug administered in a single treatment session via multiple injections into subcutaneous fat.

8.2. FORMULATION, PACKAGING AND LABELING

The RZL-012 drug is a ready to use solution to be injected into 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 and vehicle will be stored on site at monitored room temperature conditions (22 ± 7 °C) protected from light. Storage space will be separate, designated and adequately labeled as containing investigational product.

Drug product stability has successfully reached 3 years. Site inventory will be managed by the Sponsor according to accumulating stability data. Suitability of the product's expiration date must take into consideration and comply with FIFO (First In First Out) principals.

The storage conditions are summarized in Table 7.

Table 7: RZL-012 Storage Conditions

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

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

8.4.1. Dosage

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

The vehicle is available in vials of 5 mL.

8.4.2. Administration and Instructions for Use

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

The vial should be manually shaken before consumption.

1 mL Luer-lock syringes with RZL-012 solution should be filled with 30 G 1/2" sterile needle according to lipoma size (assessed by US), as described below:

Number of Subjects – Active/Placebo	19/19				
Lipoma/Nodule size – diameter (cm)	1-1.9	2-3.9	4-5.9	6-7.9	8-10
Number of Injections - Active/Placebo	2	4	8	10	12

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

8.5. ACCOUNTABILITY OF RZL-012 AND VEHICLE

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

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

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

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

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

9. ADVERSE EVENTS

9.1. ADVERSE EVENT DEFINITIONS

9.1.1. Definition of AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This definition includes any abnormalities or anomalies that were not seen at baseline or which worsened during the course of the study, if present at baseline.

9.1.2. Definition of Serious Adverse Event

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

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

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

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

9.1.3. Definition of Adverse Drug Reaction

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

9.2. ADVERSE EVENT GRADING

AE will be documented in each study visit.

AEs severity will be graded as follows:

- Mild: Sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.

- Moderate: Sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
- Severe: 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.

9.3. CAUSALITY ASSESSMENT OF ADVERSE EVENTS

All AEs will be evaluated by the investigator and assigned an estimated relationship to the RZL-012 investigational product. The terms "related" or "non-related" refer to the association with the use of the investigational product, as defined below in Table 8.

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 8).

Table 8: Definition of Causality

TERM	DEFINITION
Non-related	This category applies to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.)
Related	This category applies to those AEs which, after careful medical consideration at the time they are evaluated, are felt with high degree of certainty to be related to the study procedures/investigational product.

9.4. ADVERSE EVENT REPORTING AND MONITORING REQUIREMENTS

9.4.1. General

All AEs, serious and non-serious, will be fully documented in both source documents and CRFs as described in Section 5.1.14, and each AE will be assessed in light of its clinical significance. For each AE, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship to the investigational drug, i.e., causality assessment, for each AE.

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

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

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

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

9.4.2. SAE Reporting

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

Sponsor contact details for SAE reporting:

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

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

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

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

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

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

10. STATISTICAL CONSIDERATIONS

10.1. STUDY DESIGN AND OBJECTIVE

The statistical analysis described below relates to the place-controlled phase of the study.

This study will be a double blinded, randomized, placebo-controlled, Phase 2b trial to assess RZL-012 efficacy on DD subjects. A total of 38 eligible subjects will be randomized to receive a single injection session with either RZL-012 or placebo (vehicle) in a 1:1 ratio and will be monitored for safety and efficacy during 84 days of follow up.

Once study ends and codes opened, the 19 placebo-treated subjects will be offered to be treated with RZL-012 and followed up for an additional 84 days. The efficacy and safety results that will be collected during the open label extension phase of the study will be reported in a separate statistical report.

Primary end point:

Average percent reduction in lipoma/nodule height on day 84 after injection vs baseline, in the RZL treated group as compared to the placebo treated group. Lipoma height will be assessed by ultrasound.

Key secondary Endpoint:

Average percent reduction in lipoma/nodule pain on day 84 after injection vs baseline, in the RZL-012 treated group as compared to the placebo treated group. Lipoma pain will be assessed by the Comparative Pain Scale.

Additional secondary endpoints:

1. RZL-012 injection safety and tolerability in DD subjects.
2. Percent responding lipomas/nodules (a responding lipoma is defined as having more than 75% height reduction on day 84 after injection vs baseline), in the RZL-012 treated group as compared to the placebo treated group.

10.2. STUDY ENDPOINTS

10.2.1. Analysis of Efficacy for Primary Endpoint

- **Analysis per patient (based on 4-8 lipomas/nodules per patient)**

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule height at day 84 after injection vs. baseline.

Analysis of covariance (ANCOVA) model will be applied in order to identify covariate parameters suspected as related to reduction in lipoma/nodule height and in order to test the differences in percent reduction of lipoma/nodules height between the treatment groups adjusted to the above covariates.

- **Analysis per lipoma/nodule (based on 4-8 lipomas/nodules per patient)**

The MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference between the groups in percent reduction of lipoma/nodule height from baseline to day 84 and adjusted for the above covariates as appropriate.

10.2.2. Analysis of Efficacy for key secondary Endpoint

- **Analysis per patient (based on 4-8 lipomas/nodules per patient)**

The two-sample T-test or Non-parametric Wilcoxon-Mann-Whitney Rank sum test for independent samples (as is appropriate) will be applied for testing the statistical significance of the difference between study groups in percent reduction of lipoma/nodule pain at day 84 after injection vs. baseline.

Analysis of covariance (ANCOVA) model will be applied in order to identify covariate parameters suspected as related to reduction in lipoma/nodule pain and in order to test the differences in percent reduction of lipoma/nodules pain between the treatment groups adjusted to the above covariates.

- **Analysis per lipoma/nodule (based on 4-8 lipomas/nodules per patient)**

The MMRM model (Mixed-effect model for repeated measures) will be applied for analyzing the difference between the groups in percent reduction in local pain score at day 84 vs. baseline between the study groups adjusted for the above covariates as appropriate.

10.2.3. Analysis of other Secondary Endpoints

- **Analysis of Safety**

Safety data from the study will be summarized descriptively by treatment. The incidence of intolerable side effects will be presented by treatment.

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. Draize scores will be presented in tabular format by visit and treatment. Serious adverse events (SAEs) will be described in narratives as part of the study report.

- **Analysis of Efficacy**

Clearance of nodules: (Analysis per Lipoma based on 4-8 lipomas per patient):

95% Confidence Interval (CI) will be calculated for the proportion of responding nodules (response will be defined as achieving a reduction in lipoma height of at least 75% vs. baseline) by study groups.

GEE (Generalized Estimating Equations) model will be applied for testing the statistical significance of the difference in percent of responding nodules (nodules with at least 75% clearance at day 84 vs. baseline) between the study groups, with adjustment to suspected confounders.

10.3. SAMPLE SIZE JUSTIFICATION

Based on primary endpoint:

The rationale for sample size calculation was based on interim data from Raziel's open label phase 2a study (Study #RZL-012-FD-P2aUS-001) in which reduction in lipoma/nodule height of about 55% was demonstrated in the treatment group. Raziel's phase 2a study did not include a placebo group but studies reported by other groups (15,16) show an average reduction from baseline in lipoma/nodule height of about 7% in the placebo group. Taking these numbers into consideration Raziel expect an effect size of 0.96 (effect size = expected effect size in treated (0.55) – expected effects size in placebo group (0.07)/expected standard deviation (0.5)).

Sample size justification:

A sample size of 19 in each group (total sample size of 38) will have 80% power to detect a difference in means of 48 (the difference between a Group 1 mean, μ1, of 55 and a Group 2 mean, μ2, of 7) assuming that the common standard deviation is 50 using a two-group t-test with a 0.05 two-sided significance level.

Based on key secondary endpoint:

The rationale for sample size calculation was based on data from our open label phase 2a study (Study #RZL-012-FD-P2aUS-001) in which reduction in lipoma/nodule pain score of about 76% was demonstrated in the treatment group. Our phase 2a study did not include a placebo group but pain studies reported by other groups (17) show a range of reduction in pain score from +10% - - 60% in the placebo group. Based on Geography, study size and length we selected an expected reduction from baseline of 25% in lipoma pain in our placebo group. Taking these numbers into consideration we expect an effect size of 1.02 (effect size = expected effect size in treated (0.76) – expected effects size in placebo group (0.25)/expected standard deviation (0.5)).

Sample size justification:

A sample size of about 19 in each group (total sample size of 38) will have 80% power to detect a difference in means of 51 (the difference between a Group 1 mean, μ1, of 76 and a Group 2 mean, μ2, of 25) assuming that the common standard deviation is 50 using a two-group t-test with a 0.05 two-sided significance level.

10.4. STATISTICAL ANALYSIS

10.4.1. General

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

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

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

All tests will be two-tailed, and a p value of 5% or less will be considered statistically significant.

Subject Disposition

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

Note that the actual study duration is for a period of maximum 3.5 months, with efficacy analyses being conducted at Day 28, 56, and 84 visits.

At the end of the period, when the follow up of subjects will be completed, randomization codes will be opened.

Placebo subjects who would like to be treated with RZL-012 at the end of the study will be injected (within a period of 30 days from codes opening) and will be followed up for efficacy for additional 84 days. The efficacy information that will be collected for the open label extension study will not be included in the randomized double blinded study report but will be used for internal information.

10.4.2. 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 visit.

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

10.4.3. Efficacy Analysis

The change from baseline lipoma height will be presented in tabular form by treatment group.

The changes from baseline in pain score as a function of treatment group will be presented in tabular form per treatment group.

10.4.4. Safety and Tolerability

Safety analyses will be descriptive in nature.

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

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

10.5. HANDLING OF MISSING DATA

No imputation of missing data will be performed.

10.6. INTERIM ANALYSIS

No interim analysis is planned.

11. DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

11.1. DATA COLLECTION AND REPORTING

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

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

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

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

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

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

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

11.2. RECORD KEEPING

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

11.3. SOURCE DATA AND SOURCE DOCUMENTS

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

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

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

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

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

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

11.4. STUDY MONITORING

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

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

11.5. CONFIDENTIALITY, DATA DISCLOSURE, AND PUBLICATION

In order to protect subject confidentiality, a consecutive identification number will be attributed to each subject enrolled to the trial, at each site. In order to avoid identification errors, this number 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 5.1.1.

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.

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APPENDIX I: TRIAL SCHEDULE OF EVENTS

	Double Blind, Randomized, Placebo Controlled							**Open Label extension for Placebo subjects (will be done within 30 days of study completion)**					
Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Visit Schedule (Day 0 to 84)**					
Study Day	**Day (-14) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**Day [d] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**
Signed informed consent	X												
Medical history	X												
Physical Exam	X				X	X		X			X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy kit test (women)[b]		X											
Vital signs	X	Pre[c] X post [c]	X		X	X		Pre[c] X post [c]	X		X	X	
Injection of RZL-012/Placebo		X						X					
ECG	X		X		X			X	X		X		
Serology assay	X												
Draize Score		Pre [c] X post [c]	X		X	X	X	Pre [c] X post [c]	X		X	X	X
Ultrasound measure of lipomas	X	X[e]			X	X	X	X			X	X	X
Photography of lipomas	X	X[e]			X	X	X	X			X	X	X
Serum chemistry and hematology	X		X		X			X	X		X		
Urinalysis	X		X		X			X	X		X		

	Double Blind, Randomized, Placebo Controlled							**Open Label extension for Placebo subjects (will be done within 30 days of study completion)**					
Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Visit Schedule (Day 0 to 84)**					
Study Day	**Day (-14) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**Day [d] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**
Lipid profile	X		X					X	X				
Pain assessment of each lipoma		X			X	X	X	X			X	X	X
QOL questionnaire		X					X	X					X
AEs assessment		X	X	X	X	X	X	X	X	X	X	X	X

a. Day 0 defines the day of RZL-012/placebo injection in the double blinded randomized study

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

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

d. Day 0 defines the day of RZL-012 injection in the open label study

e. In case of screening visit that will be conducted only one day before Baseline, ultrasound and photography at Baseline visit is optional. The ultrasound parameters and photography collected at screening will be used at Baseline visit.

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: SF-36 QUALITY OF LIFE QUESTIONNAIRE

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

☐Excellent ☐Very Good ☐Good ☐Fair Poor

Compared to one year ago, how would you rate your health in general now?

☐Much better now than one year ago
☐Somewhat better now than one year ago
☐About the same
☐Somewhat worse now than one year ago
☐Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these
activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

☐Yes, Limited a lot ☐Yes, Limited a Little ☐No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Lifting or carrying groceries

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Climbing several flights of stairs

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Climbing one flight of stairs

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Bending, kneeling, or stooping

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Walking more than a mile

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Walking several blocks

☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all

Walking one block
☐Yes, Limited a Lot ☐Yes, Limited a Little ☐No, Not Limited at all
Bathing or dressing yourself
☐Yes, Limited a Lot ☐Yes, Limited a Little ☐ No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as
a result of your physical health?

Cut down the amount of time you spent on work or other activities
☐Yes ☐No
Accomplished less than you would like
☐Yes ☐No
Were limited in the kind of work or other activities
☐Yes ☐No
Had difficulty performing the work or other activities (for example, it took extra effort)
☐Yes ☐No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as
a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
☐Yes ☐No
Accomplished less than you would like
☐Yes ☐No
Didn't do work or other activities as carefully as usual
☐Yes ☐No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
☐Not at all ☐Slightly ☐ Moderately ☐ Severe ☐ Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?
☐None ☐Very Mild ☐ Mild Moderate ☐ Severe ☐Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

☐Not at all ☐A little bit Moderately ☐ Quite a bit Extremely

ENERGY AND EMOTIONS:

These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?

☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Have you been a very nervous person?

☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Have you felt so down in the dumps that nothing could cheer you up?

☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Have you felt calm and peaceful?

☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Did you have a lot of energy?
☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Have you felt downhearted and blue?
☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Did you feel worn out?
☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Have you been a happy person?
☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

Did you feel tired?
☐All of the time
☐Most of the time
☐A good Bit of the Time
☐Some of the time
☐A little bit of the time
☐None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

☐All of the time
☐Most of the time
☐Some of the time
☐A little bit of the time
☐None of the Time

GENERAL HEALTH:

How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
☐Definitely true ☐Mostly true ☐Don't know ☐Mostly false ☐Definitely false
I am as healthy as anybody I know
☐Definitely true ☐Mostly true ☐Don't know ☐Mostly false ☐Definitely false
I expect my health to get worse
☐Definitely true ☐Mostly true ☐Don't know ☐Mostly false ☐Definitely false
My health is excellent
☐Definitely true ☐Mostly true ☐Don't know ☐Mostly false ☐Definitely false