Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	04-April-2019	Original Release	Alexandra Perez-Alterman , Senior Biostatistician
2.0	02-May-2019	Update following Raziel.Ltd comments	Alexandra Perez-Alterman , Senior Biostatistician
3.0	20-May-2019	Update following Raziel.Ltd comments	Alexandra Perez-Alterman , Senior Biostatistician

Statistical Analysis Plan

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

Protocol Number RZL-012-FD-P2aUS-001

TABLE OF CONTENTS

SIGNATURES PAGE

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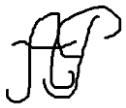

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1. DEFINITIONS AND/OR ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
BAT	Brown-like adipose tissue
BMI	Body Mass Index
BUN	Blood urea nitrogen
°C	Degrees Celsius
CBC	Complete blood count
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CK-MM	Creatine Kinase - Muscle
C_{max}	Maximum observed concentration
CNS	Clinically not significant
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CRP	C-reactive protein

CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
EF	Efficacy analysis set
FDA	Food and Drug Administration
FFA	Free fatty acids
FIFO	First In First Out
FOB	Functional Observational Battery
GLP	Good Laboratory Practice
GTTP	Gamma-glutamyltransferase
HbSAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LDH	Lactate dehydrogenase

LPL	Lipoprotein lipase
MEDDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NOAEL	No observed adverse effect level
NORD	National Organization for Rare Disorders
PI	Principal Investigator
PK	Pharmacokinetics
PKA	PK Analysis set
PT	Prothrombin time
PTT	Partial thromboplastin time
QA	Quality Assurance
QOL	Quality of life
RBC	Red blood cells
RDW	Red cell distribution width
SA	Safety analysis set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SAT	Subcutaneous adipose tissue
SC	Subcutaneous
SFM	Subcutaneous fat mass
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Terminal half-life
TAG	Triacylglycerols

TG	Triglycerides
TLA	Tumescent Liposuction (Local Anesthesia)
T_{max}	Time of maximum observed sample concentration
UCP1	Uncoupling protein 1
US/USA	United States/United States of America
WAL	Water Assisted Liposuction
WAT	White adipose tissue
WBC	White blood cells
WHO	World health organization

2. PURPOSE

2.1 The purpose of this document is to describe in detail the Statistical Analysis Plan of clinical study procedures carried out by Medistat Ltd.

2.2 This document serves Medistat Ltd. as a guiding document for all statistical analyses performed at the end of each clinical study.

2.3 This SAP is specific to Raziel Therapeutics Ltd., study RZL-012-FD-P2aUS-001.

2.4 This SAP aims to provide details on: sample size calculation, efficacy analyses and safety analyses.

3. SCOPE

3.1 This document applies to all members of the statistical & data management units in Medistat Ltd.

3.2 This document includes the main and interim study trial analysis.

4. RESPONSIBILITIES

4.1 Medistat Ltd. Responsibilities

The following personnel are responsible for these activities:

Activities	Responsible and accountable	Title
Statistical Analysis Plan (SAP)	Alexandra Perez-Alterman	Senior Biostatistician & SAS Programmer
Statistical Report and listing appendix	Alexandra Perez-Alterman	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of SAP and programs	David Israel	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of final report	Shimrit Herbst	Quality & Data Assurance Manager

4.2 Raziel Therapeutics's Responsibilities

4.2.1 To review and approve the SAP and related documents prior to database lock.

4.2.2 To review and approve the draft and final statistical report and listing appendix.

5. PROCEDURE

5.1 Introduction

5.1.1 This Statistical Analysis Plan (SAP) is based on the study protocol version 7, dated 03 January, 2019.

5.1.2 This Statistical Analysis Plan (SAP) contains details of the statistical analyses that will be performed, providing a more detailed description of the approach defined in the study protocol. Definitions of variables and populations used for the analyses are also included. The SAP will be finalized and signed prior to hard lock of the database.

5.1.3 General output specifications are provided; examples are given of calculations of derived variables.

5.2 Rationale

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

5.2.2 Cohort 1- will be comprised of subjects with Dercum's disease. All subjects will be injected with RZL-012. Dosing will be calculated according to the size of the nodule (diameter) as determined by ultrasound: 5mg/cm2 reaching a maximal dose of 40 mg RZL-012 per subject (1/6.25 the NOAEL based on the Human Dose Equivalent [HED] GLP Toxicology studies).

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

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

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

5.3 Study Objectives and Endpoints

5.3.1 Primary Objective

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

5.3.2 Secondary Objective

5.3.2.1 For lipedema subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline as assessed by leg circumference above the knee assessments and by the reduction in nodules size and/or numbers assessed by ultrasound.

5.3.2.2 For Dercum's disease subjects - The reduction in local subcutaneous fat in the injection site region as compared to baseline assessed by the reduction in nodules size and/or numbers by ultrasound.

5.3.2.3 Extended duration of the fat reduction effect. To that end, ultrasound images and circumference measurement will be followed for 56 days.

5.3.2.4 Elucidation of the tissue changes by ultrasound of the injection site to include reduction in fat thickness and nodular quality.

5.3.2.5 Improvement in local pain as measured by Comparative Pain Scale and by the reduction in the use of analgesics.

5.3.2.6 Improvement in QOL and function in lipedema subjects as measured by questionnaire (such as The Lower Extremity Functional Scale (LEFS)).

5.4 Overall study design and plan

5.4.1 Study Design

5.4.1.1 Six subjects in cohort 1, all assigned to the RZL-012 treatment group will be dosed at a maximal dose of 40 mg RZL-012 (approximately 1/6.25th the NOAEL as determined in the GLP toxicology study). Dosing will be calculated according to the size of the nodule (diameter) as determined by ultrasound in a dose of 5mg/cm2:

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

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

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

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

5.4.2 Schedule of Assessments

Study Procedure	**Screening Day**	**Baseline (Treatment)**		**Visit Schedule (Days 1 to 28)**					**Follow-up**
Study Day[a]	**Day[a]-(-14) through Day (-2)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56**
Signed informed consent	X								
Medical history	X								
Concomitant Medication	X								
Complete physical exam	X							X	
Pain measurement	X					X		X	X
For lipedema subjects - QOL measurement	X					X		X	X

Serology assays (HbSAg, HCV, HIV)	X				
Urine Drug Screen	X				
Height and weight	X				
For Dercum's disease subjects – ultrasound assessing nodules size (diameter) and quality	X				
For lipedema subjects – assessing fat thickness and nodular quality by ultrasound.	X				
For lipedema subjects – measurement of leg circumference above the knee	X	Pre [c] X			
For lipedema subjects – ultrasound assessing nodules to be injected		Pre [c] X			
For Dercum's disease subjects – ultrasound re-assessing nodules size		Pre [c] X			
Photography of site of injection	X		X		X
Serum Chemistry, Hematology [b]	X	Pre [c] X	X	X	X
Urinalysis	X				
Draize score at the injected site [d]	X	Pre [c] X post [c]	X		X

Vital signs [e]	X	Pre [c] X post [c]	X		X
Injection of RZL-012		X			
ECG [f]	X	X post [c]	X		
Pulse rate [g]		X post [c]	X		
Subjects diary recording of analgesics use	X	X	X	X	X
AE assessment			X----------		-------

a. Study day is based on Day 0 defined as the day of RZL-012 injection.
b. CBC, coagulation, serum chemistry analysis, renal and liver function, urinalysis, CPK, amylase measurement: before injection,14d and 28d following injection
c. Pre/post – refers to before/after injection respectively
d. Draize score evaluation: before injection, 2h, 24h and 7d, 14d, 21d and 28d following injection
e. Vital signs measurement: before injection, 2h, 24h and 7d, 14d, 21d and 28d following injection
f. ECG is to be performed in triplicate for all measurements in given time point: 4h, 8h, 24h following injection
g. Pulse rate measurements at given time points: 1h, 2h, 4h, 8h, 24h following injection in the opposite hand of blood sampling

5.4.3 Randomization, Blinding and Un-blinding

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

5.5 Selection of study population

5.5.1 Study Population

5.5.1.1 Post-menopausal women no more than 65 years old, with lipedema involving substantial fat above the knee or nodular Dercum's disease in such women and in men 20- 65 years with nodular Dercum's disease.

5.5.2 Rationale Sample Size Calculation

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

5.6 Statistical Analysis Software and Data Management

5.6.1 Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® version 9.3 or higher for Windows. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

5.6.2 Data Management

5.6.3 Data management for the study is performed by Medistat.

5.6.4 Medical Coding

5.6.5 Concomitant medications entered into the database are coded using the WHO (World Health Organization) Drug Public Website Dictionary named WHOCC-ATC/DDD index, which employs the Anatomical Therapeutic Chemical classification system.

5.6.6 Adverse events are coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) terminology.

5.6.7 Medical history events are coded using the most updated version of Medical Dictionary for Regulatory Activities (MedDRA) terminology

5.6.8 Handling of Missing data

5.6.9 No imputation of missing data will be performed

5.7 Subject Population for analyses

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

5.7.2 All enrolled subjects receiving at least one study drug injection are considered evaluable for the SA set.The SA analysis set will serve as the principal data analysis set for the analyses of the safety endpoints.

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

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

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

5.8 Statistical Analysis

5.8.1 General

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

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

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

5.8.5 The data is analyzed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina).

5.8.6 Statistical methods presented in the SAP may be slightly different from those that are presented in the protocol. Differences are clearly stated and the SAP supersedes the protocol only with regard to the way data will be handled and analysed.

5.8.7 Subject Disposition

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

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

5.8.10 Demographic and Baseline Characteristics

5.8.11 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.

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

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

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

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

5.8.16 Safety and Tolerability

5.8.17 Safety analyses will be descriptive in nature.

5.8.18 All reported AEs will be coded to a standard set of terms using MedDRA coding dictionary (V22.0 or higher) treatment.

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

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

5.8.21 Concomitant medication verbatim terms (as recorded on the CRFs) will be coded to Anatomical Therapeutic Chemical (ATC) Level 2 and 4 using the World Health Organization (WHO) dictionary.

6. RELATED DOCUMENTS (OPTIONAL)

6.1 Study Protocol: Protocol V7 - RZL-012-FD-P2aUS-001.7_CLEAN.docx

7. RELATED FORMS (OPTIONAL)

Not Applicable

8. REFERENCES

Not Applicable

9. APPENDICES (OPTIONAL)

9.1 APPENDIX I: TABLE SHELLS

14.1 Demographic Data

Table 14.1-1: Disposition of Subjects

Table 14.1-2: Analysis populations

Table 14.1-3: Demographic Data (Part 1 of 2)

Table 14.1-3: Demographic Data (Part 2 of 2)

Table 14.1-4: Medical History

Table 14.1-5: Disease-Related Medical History

14.1-6: Disease characteristics

Table 14.1-6-1: Dercum's cohort lipoma type

Table 14.1-6-2: Lipedema disease characteristics (Part 1 of 2)

Table 14.1-6-2: Lipedema disease characteristics (Part 2 of 2)

14.2 Drug administration

Table 14.2-1 Drug administration

14.3 Efficacy Assessment

Table 14.3-1 Pain by comparative scale by cohort

Table 14.3-2 Reduction in Pain from baseline by visit

Table 14.3-3 Relative Change in local pain

14.3-4 Dercum's disease cohort

Table 14.3-4-1 Number of Lipomas by visit

Table 14.3-4-2 Reduction of number of Lipomas from baseline by visit

Table 14.3-4-3 Relative Change in Number of lipomas

Table 14.3-4-4 Size of lipomas by visit and type

9.2 APPENDIX II: LISTINGS SHELLS

16.2.1 Subject Disposition

Listing 16.2.1-1: Subject Disposition

Listing 16.2.1-2: Visit dates per subject

Listing 16.2.1-3: Unscheduled Visit

16.2.2 Protocol Deviations

Listing 16.2.2-1: Inclusion/Exclusion criteria violations

16.2.3 Demographic Data and Baseline Assessments

Listing 16.2.3-1: Demographic Data

Listing 16.2.3-2: Medical History

Listing 16.2.3-3: Disease-Related Medical History

16.2.3-4: Disease characteristics

Listing 16.2.3-4-1: Dercum's disease cohort lipoma type

Listing 16.2.3-4-2: Lipedema cohort disease characteristics

16.2.4 Compliance/Exposure/Drug Concentration Data

Listing 16.2.4-1: Injection of RZL-012 (Part 1 of 2)

Listing 16.2.4-1: Injection of RZL-012 (Part 2 of 2)

16.2.5 Individual Efficacy/Response Data

Listing 16.2.5-1: Comparative pain for both cohort

16.2.5-2 Ultrasound and measurements Dercum's cohort

Listing 16.2.5-2-1: Number of Lipomas

Listing 16.2.5-2-2: Lipomas description

Listing 16.2.5-2-3: Size of Lipomas

16.2.5-3 Ultrasound and measurements Lipedema cohort

Listing 16.2.5-3-1: Number of Injected Fat Locations

Listing 16.2.5-3-2: Fat tissue description

Listing 16.2.5-3-3: Fat tissue description

Listing 16.2.5-3-4: Thickness of Fat Tissue

Listing 16.2.5-3-5: Thickness of Fat Tissue - Shift table

Listing 16.2.5-3-6: Average reduction in Thickness of Fat Tissue