Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	01/06/2022	Original Release	Einan Farhi , Senior Biostatistician

Statistical Analysis Plan

Study Title:

A Phase 2 Clinical Trial Comprised of a Double-Blind, Placebo-Controlled Phase Followed by An Open-Label Phase to Evaluate the Safety and Efficacy of RZL-012 in Subjects Seeking Fat Reduction in the Flanks (RZL-012-FL-P2US-001)

TABLE OF CONTENTS

SIGNATURES PAGE

Author : Einan Farhi

Senior Biostatistician & SAS programmer

MediStat Ltd. Date: 01/06/2022

Reviewer: David Israel

Senior Biostatistician & SAS programmer

MediStat Ltd. Date: 01/06/2022

Approved by: Racheli Gueta

Raziel Therapy Ltd. Date: 6/1/2022

1. DEFINITIONS AND/OR ABBREVIATIONS

AE	Adverse event
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiograms
GAIS	Global Aesthetics Improvement Scale
ICF	Informed Consent Form
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-Protocol
PK	Pharmacokinetics
QA	Quality Assurance
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
WHO	World health organization

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to describe in detail the statistical analyses to be conducted by Medistat Ltd on data generated from the clinical trial sponsored by Raziel Therapeutics Ltd. (clinical trial **RZL-012-FL-P2US-001)**.

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

3. SCOPE

This document applies to all members of the statistical & data management units in Medistat Ltd. This document includes the main study trial analyses.

4. RESPONSIBILITIES

Medistat Ltd. Responsibilities

The following personnel are responsible for these activities:

Activities	**Responsible and accountable**	**Title**
Statistical Analysis Plan (SAP)	Einan Farhi	Senior Biostatistician & SAS Programmer
Statistical Report and listing	Einan Farhi	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of SAP and programs	David Israel	Senior Biostatistician & SAS Programmer
Quality Assurance (QA) of final report	David Israel	Quality & Data Assurance Manager

Raziel Therapeutics's Responsibilities

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

5. PROCEDURE

- Introduction

This Statistical Analysis Plan (SAP) is based on **RZL-012-FL-P2US-001** study protocol version 1.0, dated 22 November 2021

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.

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

- Study Objectives and Endpoints

Primary Objective

To assess safety and tolerability of a single RZL-012 injection session into the flank.

Secondary Objectives:

1. To evaluate the efficacy of RZL-012 treatment versus placebo treatment on fat reduction in the flanks
2. To assess the safety of a second dose of RZL-012.

Primary Endpoints:

• To evaluate safety following a single injection session of RZL-012 vs. placebo into the flanks based on AEs, laboratory tests, ECG, and skin irritancy.

- Adverse Events (AEs) – The incidence and percentage of patients experiencing AEs in each of the treated flanks.
- Laboratory tests – The percent of abnormal clinical significant observations made following treatment.
- ECG – Change from baseline of ECG results.
- The incidence and percentage of patients experiencing skin irratancy following injections in each treated flank.

Secondary Endpoints:

- Comparison of the proportion of flanks having an improvement as indicated by a score of 0 to 6 according to the Physician Global Assessment Scale (GAIS) in RZL-012-treated flanks vs placebo-treated flanks.
- Comparison of the proportion of subjects who are satisfied with treatment results as indicated by a yes/no satisfaction questionnaire in RZL-012-treated flanks vs placebo-treated flanks.
- Comparison of the mean reduction in volume at 12 weeks post treatment vs. baseline for each of the treated flanks, as measured by 3D images using the Canfield 3D system in RZL-012-treated flanks vs placebo-treated flanks.
- Ability of blinded reviewers to correctly identify, per patient, the flank treated with test compound (active) vs the flank treated with vehicle (placebo). Success will be defined as at least 70% correct identification vs the expected 50% correct identification based on random guessing.
- Evaluate safety following a second dose of RZL-012 based on AEs, laboratory tests, ECG, and skin irritancy.
- Characterization of RZL-012 pharmacokinetic (PK) profile

- Study Design

This clinical trial is comprised of a double-blind, placebo-controlled phase followed by an open-label phase. The study will be conducted in a single center.

The double-blind, placebo-controlled phase of the trial will consist of a screening period, baseline visit and a 12-week post-treatment follow-up period. At the baseline visit, each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will receive multiple injections in a single session of RZL-012 or placebo. Blood samples will be collected for 6 of the 12 subjects for PK analyses. All subjects will be followed up for 12 weeks after the single treatment session.

Upon completion of the double-blind phase of the study, and the opening of codes subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo. Consenting subjects will be followed for safety and efficacy for an additional 12 weeks.

In both the double-blind and open-label phases of the study, subjects will be monitored for adverse events (AEs). Subjects will return to the site for visits at 1 week, 4 weeks, 8 weeks, and 12 weeks post treatment and will be monitored for safety and efficacy during these visits.

Subjects who will be collected with PK will return to the clinic at Day 1 post injection for further PK samples.

The dimensions of flanks will be measured using 3D images and volumetric calculations using Canfield 3D images.

At the start of the double-blind, placebo-controlled phase of the trial each flank (right and left) of each study participant will be randomized into either the active RZL-012 treatment group or the placebo group and each flank will be treated with multiple injections in a single injection session in accordance with the table below:

	RZL-012 (50mg/mL DP injectable solution)	Placebo (Injectable sterile solution)
Randomized Right or left flank	12	12
Single Treatment*	55 injections at 7.5mg/0.15mL per each injection point – A total of 412.5 mg/8.25 mL total dose per flank	55 injections at 0.15mL per each injection point – A total volume of 8.25 mL total dose per flank
* 55 injections is the maximum number of injections. In case of smaller flanks, the number of injections may be lower.		

Upon completion of the double-blind phase of the study, and the opening of codes, subjects will be offered RZL-012 open-label treatment in the flank previously treated with placebo in the same manner as described in the table above.

Treatment will cover the area of each randomized flank. A surface area of 15 cm x 6 cm will be chosen for treatment. Flanks will be injected with RZL-012/placebo with the needle pointing perpendicular (90°) to skin surface. An ice pack will be placed on the injected area for pain relief immediately after injections are completed. Subjects will remain in injection position for an additional 10 minutes after dosing.

- Schedule of Assessments

Study Procedure	**Screening Day**		**Double Blind Phase**					**Open Label Phase**				
Study Day	**Day -28 through Day -1**	**Baseline Day 0 [a]**	**Day 1 [e]**	**Week 1 (±2 days)**	**Week 4 (±5 days)**	**Week 8 (±5 days)**	**Week 12 (±5 days)**	**Day 0 [a]**	**Week 1 (±2 days)**	**Week 4 (±5 days)**	**Week 8 (±5 days)**	**Week 12 (±5 days)/ Final visit**
Signed informed consent	X											
Eligibility criteria	X	Pre[c] X										
Medical history	X											
Physical Exam	X						X					X
Concomitant Medication	X	X		X	X	X	X	X	X	X	X	X
Pregnancy ß-hCG	X											
Weight measurements	X	X			X	X	X			X	X	X
Pharmacokinetics blood samples		X	X									
Hematology and Chemistry[b]	X			X	X		X		X	X		X
ECG	X			X	X		X		X	X		X
Vital signs	X	Pre[c] X post[c]		X	X	X	X	Pre[c] X post[c]	X	X	X	X
Injection of RZL-012 or placebo		X						X				
Physician's GAIS					X	X	X			X	X	X
Subject Satisfaction questionnaire					X	X	X			X	X	X
2D Standardized photography	X			X	X	X	X	X	X	X	X	X
3D photography	X			X	X	X	X	X	X	X	X	X
AEs[d]			X	X	X	X	X	X	X	X	X	X

a. Day 0 defined as the day of RZL-012 or placebo injection.
b. In case of clinically significant values at any visit, an unscheduled visit will be added
c. Pre/post – refers to before/after injection, respectively
d. AEs will be recorded throughout the study until the final study visit. In case of ongoing AEs at the final study visit an unscheduled visit will be scheduled for further follow-up. Treatment area will be evaluated including, but is not limited to, evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.
e. Day 1 visit is only for subjects who volunteer for PK blood samples

- Rationale Sample Size Calculation

Twelve adult volunteers of age 18 to 65 years with visible and palpable fat in the flanks will be enrolled into this study. During the double-blind phase of the study, each subject will be treated in both flanks, one with RZL-012 and one with placebo. Thus, the sample size would be 12 subject with 24 flanks. This will result in a comparison of 12 active treated flanks vs. 12 placebo treated flanks.

As the study primary objective is to indicate safety and is only expected to show trends in of the efficacy endpoints, no formal sample size calculation has been made. Therefore, p-value which may be shown in the final report, will be presented only to establish trends.

- Statistical Analysis Software and Data Management

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® version 9.4 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.

- Data Management

Data management for the study is performed by Medistat.

- Medical Coding

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.

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

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

- Handling of Missing data

Every effort will be made to obtain all data from all subjects who have been enrolled, to minimize missing data.

- Subject Population for analyses

The Intent-to-treat population (ITT) will consist of all enrolled subjects who received the study treatment, (exposed population), including subjects prematurely withdrawn. The ITT population will serve as the principal data analysis set for analyses of efficacy and safety endpoints. Flanks will be analyzed according to the treatment received.

The Per-Protocol population (PP) will consist of all subject included in the ITT population who completed the study according to protocol and have no protocol deviations.

6. STATISTICAL ANALYSIS

- 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 by study group. Confidence intervals (95% degree of confidence) for proportions will be presented for selected endpoints.

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).

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.

- 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 will be fully documented in the body of the Clinical Study Report.

- Demographic and Baseline Characteristics

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

Baseline data including demographics, weight, height, BMI, prior medications, medical history and pregnancy tests will be listed and tabulated with the appropriate descriptive statistics.

Baseline safety data such as vital signs, ECG, safety laboratory assessments and physical examination will be presented along with subsequent safety values assessed during or after injections.

- Analysis of Safety for Primary Endpoints

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

- Adverse Events (AEs)

AEs will be coded using MedDRA™ and will be presented by body system. AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 5.0.

AE assessment and treatment area evaluation including, but not limited to evaluation of edema, pain, bruising, erythema, induration, numbness, paresthesia, tenderness, and pruritus.

AE data will be listed individually including the nature, body system, seriousness, severity and relationship of AEs to study drug.

The incidence of AEs and percentage of patients experiencing AEs will be tabulated by the nature of AEs (all AEs, seriousness, severity and relationship to study drug). Different features may be crossed such as severity and relationship to study drug to provide additional percentages.

The incidence and percentage of patients experiencing AEs will also be summarized by SOC and by PT within a system organ class and further by severity and relationship to treatment if needed.

Serious adverse events (SAEs) will be described in narratives as part of the study report.

- Skin irritancy

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

Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects that experienced Skin irritancy AEs related to the injection procedure between the study groups.

- Safety Laboratories

All safety laboratory parameters will be summarized using continuous variable descriptive statistics where applicable. Changes and relative changes from baseline will be calculated and summarized as well.

The normal/abnormal status and clinical signifcance of observations will be summarized using counts and percentages per treatment group and per visit.

- ECG

ECG results will be summarized in appropriate tables using descriptive statistics. Changes from baseline values will be summarized as well to indicate if there has been any change.

- Analysis of Safety following a second dose of RZL-012

For subjects who continue to the second phase an additional analysis will be presented to indicate the safety of a second dose. The course of analysis will follow the primary safety analysis but only for the period starting from the second dose and with no comparison between treatment groups.

For example, the percentage of patients and incidence of AEs will be summarized also only for the period post unblinding and only for the population which continued to the second phase (percentages will be calculated based on the new sample size).

- Analysis of Efficacy

  The secondary endpoints will be analyzed as follows:

  - Physician’s GAIS

Flank volume reduction from baseline to week 12, assessed by Physician Global Assessment score (GAIS). The proportion of flanks having an improvement as indicated by a score of 0-6 according to the Physician Global Assessment Scale (GAIS) in RZL-012 vs placebo treated flanks will be assessed.

Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of subjects for whom an improvement in GAIS was observed between treatment groups. Will be calculated along with 95% exact confidence interval by treatment group.

- Correct pre and post-treatment identification

The proportion of correctly identified photos (treated flank) by blinded reviewers will be calculated along with 95% exact confidence interval by treatment group.

- Satisfaction (Yes/No question)

The proportion of satisfied subjects will be calculated along with 95% exact confidence intervals for each treatment group. Fisher's Exact test will be applied for testing the statistical significance of the difference in percent of satisfied subjects between treatment groups.

- Reduction in Volume

The change and relative change from baseline in Flank volume as measured by photographs at 12 weeks post-treatment will be calculated per each treatment group. The Signed rank test for two means (paired observations) will be applied for testing the statistical significance of the change and relative change from baseline at week 12 in flank volume between treatment groups.

- Analysis of Exploratory endpoint

  - Characterization of RZL-012 pharmacokinetic (PK) profile

The following parameters will be evaluated for RZL-012 injection treatment :

C_{max}: Maximum measured plasma concentration over the time span specified.

T_{max}: Time to maximum measured plasma concentration. If the maximum value is observed at more than one time point, T_{max} will be defined as the first time point observed with this value.

AUC_{0-t}: The area under the plasma concentration versus time curve, from time 0 to the last measurable concentration, as calculated by the linear trapezoidal method.

AUC_{0-inf}: The area under the plasma concentration versus time curve from time 0 to infinity. AUC_{0-inf} is calculated as the sum of AUC_{0-t} and the ratio of the last measurable plasma concentration to the elimination rate constant.

k_{el} (λ_z): Apparent first-order terminal elimination rate constant calculated from a semilog plot of the plasma concentration versus time curve. The parameter will be calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase. (e.g., three or more non-zero plasma concentrations).

$T_{½}$: Apparent first-order terminal elimination half-life will be calculated as $0.693/k_{el}$.

C_{last} / λ_z: Clast is the last measurable concentration.

Other pharmacokinetic parameters may be calculated if deemed necessary.
Summary tables will be generated for all the PK variables concentration by time point and for the derived PK parameters. The individual values of for plasma concentration and PK parameters will listed by subject.

7. RELATED DOCUMENTS (OPTIONAL)

RZL-012-FL-P2US-001 Study Protocol V1.1 30 May 2022.

8. RELATED FORMS (OPTIONAL)

Not Applicable

9. REFERENCES

Not Applicable

10. APPENDICES

Not Applicable