A DOUBLE BLIND, RANDOMIZED, THREE-ARM, PLACEBO-CONTROLLED PHASE 2b STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RZL-012 IN SUBJECTS SEEKING SUBMENTAL FAT REDUCTION

NCT04867434

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Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	08/03/2022	Original Release	Alexandra Perez-Alterman , Senior Biostatistician

Statistical Analysis Plan

Study Title:

A double blind, randomized, three-arm, placebo-controlled Phase 2b study to evaluate the efficacy and safety of RZL-012 in subjects seeking submental fat reduction

Study RZL-012-SMF-P2bUS-001

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SIGNATURES PAGE

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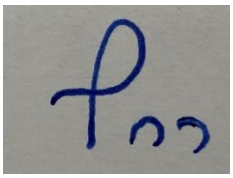

1. DEFINITIONS AND/OR ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
BMI	Body Mass Index
C-CAT	Clinical Chin Assessment Tool
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CRF	Case Report Form
ECG	Electrocardiograms
GAIS	Global Aesthetics Improvement Scale
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NOAEL	No observed adverse effect level
PI	Principal Investigator
PP	Per-Protocol
QA	Quality Assurance
QOL	Quality of life
S-CAT	Subject Self-Chin Assessment Tool
SAE	Serious adverse event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SMF	Submental fat
TEAE	Treatment emergent adverse event(s)
US/USA	United States/United States of America
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-SMF-P2bUS-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)	Alexandra Perez-Alterman	Senior Biostatistician & SAS Programmer
Statistical Report and listing	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	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-SMF-P2bUS-001**study protocol version 1.6, dated 08 March 2022

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 determine the efficacy of RZL-012 versus placebo on submental fat (SMF) reduction measured on Day 84 versus baseline using the Clinician Assessment Tool (C-CAT).

Secondary Objectives

To determine the efficacy of RZL-012 versus placebo on SMF reduction measured on Day 84 versus baseline using both the Subject Self-Chin Assessment Tool (S-CAT) and the Clinician Assessment Tool (C-CAT).;

To assess the reduction in SMF on Day 84 versus baseline using the caliper measured submental thickness and magnetic resonance imaging (MRI);

To assess the safety of RZL-012 in the treatment of SMF reduction.

Primary Endpoint

Comparison of the proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline between the RZL-012 high dose (270 mg/5.4 mL) group and the placebo group.

Secondary Endpoints:

- Proportion of subjects who have at least a 1-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group.
- Proportion of subjects who have at least a 2-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline) in the RZL-012 groups versus placebo group.
- Reduction in SMF volume by MRI (Day 84 versus screening) in the RZL-012 groups versus placebo group.
- Reduction in SMF thickness measured with caliper (Day 84 versus baseline) in the RZL-012 groups versus placebo group.Safety assessment of RZL-012 in the treatment of SMF reduction.
- safety of RZL-012 in the treatment of SMF reduction.

Exploratory endpoints:

- Physicians Global Assessment
- SMF improvement using the Global Aesthetic Improvement Scale (GAIS).
- Subject Global Self-Assessment
- SMF improvement using the Subject Global Assessment of Change Scale.
- SMF improvement using the subject's satisfaction questionnaires.
- SMF improvement using Subject's impact questionnaire.

- Study Design

This is a Phase 2b, double-blind, randomized, three-arm, placebo-controlled study that consists of a screening period, baseline period, and a randomized treatment period. Subjects receive a single treatment session that consists of multiple injections of RZL-012 or placebo into the submental area under the chin, after which they are monitored for safety and efficacy over 84 days.

Following the completion of Day 84 visit of the last subject, subjects from three (3) chosen clinical sites are followed up to a 1 year after injection to evaluate the long term safety and efficacy. The additional follow up visits are conducted at 6 and 12 months after injection.

Study participants are adult volunteers (135 subjects - 45 subjects per group) of 18 to 65 years of age who have consented to participate in this study. Each subject is randomized to either active treatment (high or low dose RZL-012) or placebo at a ratio of 1:1:1 per group and receives one of the following:

- low dose (concentration of injected solution 34 mg/mL RZL-012) of 5.1 mg/0.15 mL/injection point (32±4 injection points) that results in an average total injected dose/volume of 163.2±20.4mg/4.8±0.6 mL RZL-012.

- high dose (concentration of injected solution 50 mg/mL RZL-012) of 7.5 mg/0.15 mL/injection point (32±4 injection points) that results in an average total injected dose/volume of 240±30mg/4.8±0.6mL RZL-012.
- placebo of 0.15 mL/injection point (32±4 injection points) that results in an average total injected volume of 4.8±0.6mL.

- Schedule of Assessments

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Additional follow up of RZL-012 treated subjects (6 and 12 months after injection)**	
Study Day[a]	**Day (-28) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**6 months**	**12 months**
Signed informed consent	X								
Medical history	X								
Physical Exam[b]	X						X	X[h]	X[h]
Concomitant Medication	X	X	X	X	X	X	X		
Pregnancy ß-hCG	X								
Pregnancy urine test (women)[c]		X							
Caliper measurement of submental fat	X				X	X	X		
Weight measurements	X	X				X	X		
Hematology and Chemistry[d]	X		X	X	X		X		
ECG	X			X			X		
Vital signs	X	Pre[e] X post[e]	X	X	X	X			
Injection of RZL-012		X							
Clinician Chin Assessment Tool (C-CAT)	X	X			X	X	X	X	X

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**					**Additional follow up of RZL-012 treated subjects (6 and 12 months after injection)**	
Study Day[a]	**Day (-28) through Day (-1)**	**Day [a] 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**	**6 months**	**12 months**
Subject- Self-Chin Assessment Tool (S-CAT)	X	X			X	X	X	X	X
Physician Global Assessment Improvement Scale (GAIS) and physician global assessment	X				X	X	X		
Subject's Satisfaction questionnaire for SMF appearance	X[g]				X	X	X		
Subject's impact questionnaire	X				X	X	X		
Subject Global Assessment of Change and subject self assessment	X				X	X	X		
2D Standardized photography	X		X	X	X	X	X	X	X
MRI	X[f]						X		
AEs		X	X	X	X	X	X	X	X

a. Study day is based on Day 0 defined as the day of RZL-012 injection.
b. Including Fitzpatrick skin type, height, BMI
c. A serum (ß-hCG) pregnancy test will be administered to females of childbearing potential at screening and a urine pregnancy test will be administered at baseline prior to dosing
d. In case of clinically significant values at any visit, an unscheduled visit will be added
e. Pre/post – refers to before/after injection, respectively
f. MRI (performed during screening period) will be conducted after subject qualifies on all screening criteria within a window of 10 days from the visit in the clinic. Post-treatment period MRI will be completed 84 days (± 7 days) after the subject's last treatment session.
g. Subjects will be asked on their neck appearance satisfaction at screening visit
h. Physical exam will be done only to the treated area

- Rationale Sample Size Calculation

For the primary endpoint (proportion of high dose group subjects who have at least a 1-grade improvement from baseline to Day 84 on the C-CAT scale), the assumed true rates are 70% in the RZL-012 high dose group and 35% in the placebo group (a difference of 35 percentage points). Based on the use of a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance, 41 subjects per group are required at 90% power. In order to account for a dropout rate of up to ~9%, the planned sample size is 45 subjects per group, for a total sample size of 135 subjects.

- 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.

A subject with missing primary endpoint data will be imputed as treatment failure.

- 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. Subjects will be analyzed according to the treatment received

The Per-Protocol population (PP) will consist of all subject included in the ITT population who were rated for both S-CAT and C-CAT on both baseline and day 84 visits. The PP population will serve as a sensitivity analysis of the efficacy endpoints.

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 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).

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, taking place on or after study drug injection, 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 safety data will be presented along with subsequent safety values assessed during or after dosing.

- Analysis of Efficacy for Primary Endpoint

The proportion of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline will be calculated for the placebo group and the RZL-012 high-dose group along with 95% Confidence interval for proportion.

The Chi-Square test will be applied to test the statistical difference between the placebo group and the RZL-012 high-dose group in responder rate at Day 84. Responder rate is defined as the percentage of subject achieving at least a 1-grade improvement from baseline in C-CAT.

- Analysis of secondary Endpoints

Secondary endpoints (improvement in 1 point in S-CAT and C-CAT, improvement in 2 points in both S-CAT and C-CAT) will be tested using a two-sided test of equality of binomial proportions at the alpha=0.05 level of significance.

All other secondary endpoints will be tested using a two-sided test at the alpha=0.05 level of significance.

- The Chi-Square test will be applied to test the statistical difference between the placebo group and each of the RZL-012 dose groups in the responder rate at Day 84 where responder rate is defined as the percentage of subject achievieng at least a 1-grade improvement from baseline in both S-CAT and C-CAT.

- The change and percentage of change from baseline at Day 84 in SMF thickness measured with caliper and in SMF volume by MRI will be calculated along with 95% Confidence intervals.

The Paired T-test for two means (paired observations) will be applied for testing the statistical significance of the change and percentage of change from baseline at Day 84 in SMF thickness measured with caliper and in SMF volume by MRI within each study group.

The two-sample T-test for independent samples will be applied for testing the statistical significance of the change and percentage of change from baseline at Day 84 in SMF thickness measured with caliper and in SMF volume by MRI between each of the RZL-012 dose groups and the placebo group.

- Analysis of Exploratory endpoint

  - SMF improvement

The SMF improvement using the Global Aesthetic Improvement Scale (GAIS) , the physician Global Assessment of Change Scale, Subjects Global Self-Assessment of Change Scale, Subject Global Assessment of Change Scale, the subject's satisfaction questionnaires, and the subjects's impact questionnaire will be summarized at each timepoint and by treatment group.

- 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 of AEs to study treatment will be tabulated for all subjects combined and by treatment.

Change-from-baseline values for vital signs, clinical laboratory and ECG will be summarized. Serious adverse events (SAEs) will be described in narratives as part of the study report.

7. RELATED DOCUMENTS (OPTIONAL)

Raziel Protocol_RZL-012-SMF-P2BUS-001.6 , March 08 2022.

8. RELATED FORMS (OPTIONAL)

Not Applicable

9. REFERENCES

Not Applicable

10. APPENDICES

Not Applicable