Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	03/08/2022	Original Release	Einan Farhi , Senior Biostatistician

Statistical Analysis Plan

Study Title:

An Open-Label Phase 2 Study to Compare the Pharmacokinetics, Efficacy and Safety of RZL-012 in Chinese Subjects Seeking Submental Fat Reduction vs. Non-Chinese Subjects Seeking Submental Fat Reduction (RZL-012-SMFC-P2US-001)

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SIGNATURES PAGE

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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
C-CAT	Clinician-Chin Assessment Tool
S-CAT	Self-Chin Assessment Tool
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
SMF	Submental Fat
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-SMFC-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-SMFC-P2US-001** study protocol version 1.2, dated 26 July 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 compare the pharmacokinetic profile of RZL-012 in subjects that are dosed in the submental fat (SMF) in a Chinese vs. a non-Chinese population.

Secondary Objectives:

1. To compare the efficacy of RZL-012 in SMF reduction measured on Day 84 versus baseline using the Clinician Assessment Tool (C-CAT) in Chinese vs. non-Chinese population.
2. To determine the efficacy of RZL-012 in SMF reduction measured on Day 84 versus baseline using both Subject Self-Chin Assessment Tool (S-CAT) and the Clinician Assessment Tool (C-CAT) in a Chinese vs. a non-Chinese population.
3. To compare the reduction in SMF on Day 84 versus baseline using the caliper measured submental thickness in a Chinese vs. a non-Chinese population
4. To assess the safety of RZL-012 in the treatment of SMF reduction.

Primary Endpoints:

Characterization of RZL-012 pharmacokinetic (PK) profile in a Chinese vs. non-Chinese population based on

- Cmax - Maximum concentration achieved.
- T_{max} - Time to reach maximum concentration (hours).
- AUC_{last} – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the last measurable data point.
- $AUC_{partial}$ – The area under the concentration vs. time curve, calculated as sum of AUCs using linear trapezoidal summation from time 0 to the maximal measurement (T_{max}).
- λ_z ($Lambda_z$)- Individual estimate of the terminal elimination rate constant, will be calculated using log-linear regression of the terminal portions of the plasma concentration-versus-time curves.
- AUC_{inf} - The area under the plasma concentration-time curve extrapolated to infinity, calculated as:

  AUClast + Clast/λz, where Clast is the last measurable concentration.
- $T_{1/2}$ - Apparent terminal elimination half-life time (hours), defined as 0.693/λz.

Exploratory Endpoints:

- Comparison of the proportion of subjects in each population who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline.
- Comparison of the proportion of subjects in each population who have at least a 1-grade improvement in the S-CAT on Day 84 versus baseline.
- Comparison of the proportion of subjects in each population who have at least a 1-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline).
- Comparison of the proportion of subjects in both populations who have at least a 2-grade improvement in both the C-CAT and S-CAT (Day 84 versus baseline).
- Comparison of the reduction in SMF thickness measured with caliper (Day 84 versus baseline) in a Chinese vs. non-Chinese population
- Safety of RZL-012 in the treatment of SMF reduction.

- 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 2, open-label study that will consist of a screening period, baseline period in which subjects will receive a single treatment session and a follow-up period. The single treatment session will consist of multiple injections of RZL-012 for a maximal total dose of 270 mg into the submental area under the chin. Blood samples will be collected from all subjects for PK analyses in the first 30 hours after dosing. Subjects will thereafter be monitored for safety and efficacy for at least 84 days.

20 adult volunteers (10 Chinese and 10 non-Chinese) whose age is within 18 to 65 years who have consented to participate in this study and seek submental fat reduction will be enrolled into the study.

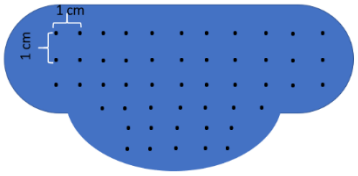
All subjects will receive a single multi-injection session of RZL-012 in accordance with the table below:

Number of subjects	N=20
RZL-012 dose	240mg±30mg/4.8 ±0.6 mL
RZL-012 Dose (mg)/volume (mL) per single injection	7.5mg/0.15mL
Number of Injections per subject	32±4

Subjects will undergo a single treatment session with 32±4 injections. The total number of injections will be 32±4 with a dose of 240±30 mg RZL-012. Each injection point will be dosed with 7.5 mg RZL-012 in a volume of 0.15 mL/injection site. The total injection volume for all groups will be 4.8 mL±0.6.

Subjects will be injected with RZL-012 perpendicularly (90°) to the skin. An ice pack will be placed on the injected area for pain relief immediately after injection. Subjects will remain seated in the injection position for an additional 10 minutes after dosing.

The injection pattern will be based on a submental area shaped grid in which the distance between rows and columns will be 1 cm, as seen in the figure below. The Investigator will choose 32±4 sequential points on the grid that will mark the injected area according to SMF fullness and convexity. The treatment area boundary: superiorly by a line 1 cm inferior to the mandibular margin, laterally by the sternocleidomastoid muscles, and inferiorly by the hyoid bone.



AEs will be collected and reviewed to evaluate the safety and tolerability of RZL-012. AE collection will begin after dosing and will end at discharge assessments on Day 84. For subjects for whom AEs are unresolved by Day 84, an unscheduled visit will be set 6-8 weeks after Day 84 to verify the resolution of the AE.

Other safety measures will include vital sign measurements, Lab parameters follow up on Day 1, 7, 28 and 84 following injection, ECG, and treatment area evaluation. Treatment area evaluations including, but not limited to evaluation of edema, bruising, dysphasia, dysphonia, erythema, dyspigmentation, induration, numbness, pain, paresthesia, pruritus, skin ulceration and necrosis, injury to the marginal mandibular nerve, vascular and nerve injury and tissue damage to nearby vulnerable anatomic structures. Concomitant medications will be recorded.

- Schedule of Assessments

Study Procedure	**Screening Day**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 84)**				
Study Day	**Day (-28) through Day (-1)**	**Day 0**	**Day 1**	**Day 7**	**Day 28**	**Day 56**	**Day 84**
Signed informed consent	X						
Medical history	X						
Physical Exam	X		X	X			X
Concomitant Medication	X	X	X	X	X	X	X
Pregnancy ß-hCG	X						
Pregnancy urine test (women)		X					X
Caliper measurement of submental fat	X				X	X	X
Weight measurements	X	X			X	X	X
Biochemistry Lab parameters	X		X	X	X		X
Pharmacokinetics		X	X				
ECG	X		X				X
Vital signs	X	Pre X post	X	X	X	X	X
Injection of RZL-012		X					

Clinician Chin Assessment Tool (C-CAT)	X	X			X	X	X
Subject- Self-Chin Assessment Tool (S-CAT)	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				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
AEs		X	X	X	X	X	X

- Rationale Sample Size Calculation

20 adult volunteers (10 Chinese and 10 non-Chinese) whose age is within 18 to 65 years who have consented to participate in this study and seek submental fat reduction will be enrolled into the study.

No formal sample size calculation was performed. The planned sample size of 10 subjects per study arm is sufficient to compare the PK profile between the 2 study populations. Any 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 (i.e. exposed population), including subjects prematurely withdrawn. The ITT population will serve as the principal data analysis set for analyses of efficacy and safety endpoints.

PK analysis will be performed on all ITT patients for whom sufficient PK data was collected.

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 study arm (Chinese vs. non-Chinese) 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 by study arm and for all subjects in ITT population.

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 Primary Endpoint

  - The characterization of RZL-012 pharmacokinetic (PK) profile and comparison in a Chinese vs. a non-Chinese population

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

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: C_{last} is the last measurable concentration.

Other pharmacokinetic parameters may be calculated if deemed necessary.

A total of 10 subjects per group will be used to compare between PK profile of both populations.

PK assessments will be compared between the 2 study populations. The individual values of for RZL-012 plasma concentration and evaluated PK parameters will listed by subject.

Summary tables will be generated for RZL-012 concentration by time point and for all derived PK parameters presenting sample size (N), mean, Standard deviation, Standard Error, Median, minimum and maximum values, Coefficient of variation (CV%) and 95% CI (Confidence Interval) for means by study arm.

Graphical displays will be generated presenting mean concentration by study arm as well as individual graphs per subject.

- Analysis of Safety Endpoints (Exploratory)

Safety data will be summarized by study arm. 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, Serious AEs (SAEs), Severe AEs AEs related to study drug, AEs that led to study/treatment discontinuation) for each study arm. 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 for each study arm.

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 study arm and per visit.

- Vital Signs

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

- ECG

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

- Analysis of Efficacy Endpoints (Exploratory)

The exploratory endpoints will be analyzed as follows:

- The proportion of subjects in each population who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline will be calculated and summarized by study arm along with 95% CIs for proportions (Fisher's Exact method).

A two-sided test of equality of binomial proportions will be applied for testing the statistical significance of the difference in percent of subjects who have at least a 1-grade improvement in the C-CAT on Day 84 versus baseline between study arms.

- The proportion of subjects in each population who have at least a 1-grade improvement in the S-CAT on Day 84 versus baseline will be calculated and summarized by study arm along with 95% CIs for proportions (Fisher's Exact method).

A two-sided test of equality of binomial proportions will be applied for testing the statistical significance of the difference in percent of subject who have at least a 1-grade improvement in the S-CAT on Day 84 versus baseline.

- The proportion of subjects in each population who have at least a 1-grade improvement in both the C-CAT and S-CAT on Day 84 versus baseline will be calculated and summarized by study arm along with 95% CIs for proportions (Fisher's Exact method).

A two-sided test of equality of binomial proportions will be applied for testing the statistical significance of the difference in percent of subject who have at least a 1-grade improvement in both the C-CAT and S-CAT on Day 84 versus baseline.

- The proportion of subjects in each population who have at least a 2-grade improvement in both the C-CAT and S-CAT on Day 84 versus baseline will be calculated and summarized by study arm along with 95% CIs for proportions (Fisher's Exact method).

A two-sided test of equality of binomial proportions will be applied for testing the statistical significance of the difference in percent of subject who have at least a 2-grade improvement in both the C-CAT and S-CAT on Day 84 versus baseline.

- SMF thickness measured with caliper will be summarized by study visit (Screening, Day 28, Day 56, Day 84) and by study arm using continuous descriptive statistics. Change and relative change from baseline will be calculated and tabulated in the same manner.

The Paired T-test or Signed rank test for two means (paired observations) (as is appropriate) will be applied for testing the statistical significance of the reduction (change and relative change from baseline) in SMF thickness measured with caliper (Day 84 versus baseline) in each study arm.

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 in reduction in SMF thickness measured with caliper (Day 84 versus baseline) between Chinese population and non-Chinese population.

The additional exploratory endpoints will be analyzed as follows:

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 subject's impact questionnaire will be summarized at each timepoint and by study group.

- The physician global assessment will be summarized using categorical descriptive statistics by study visit for each study arm. Shift from baseline will be evaluated and tabulated in the same manner.

- The Physician Global Assessment Improvement Scale (GAIS) will be summarized using categorical descriptive statistics by study visit for each study arm.

- The Subject Global Self-Assessment scale will be summarized using categorical descriptive statistics by study visit for each study arm. Shift from baseline will be evaluated and tabulated in the same manner.

- The Subject Global Assessment of Change Scale will be summarized using categorical descriptive statistics by study visit for each study arm.

- Subject’s satisfaction questionnaires answers will be summarized using desciptive statistics by study visit for each study arm. Shift from baseline will be evaluated and tabulated in the same manner.

Two Subject satisfaction binary variables will be defined for every subject in the ITT population based on the satisfaction questionnaire for each one of the questions:

1. Subjects who at any point in time answered "Extremely Satisfied" or "Satisfied" (Grades 0,1).
2. Subjects who at their last assessment answered "Extremely Satisfied" or "Satisfied" (Grades 0,1).

Subjects with no assessment will be considered as non-responders. The proportion of satisfied subjects (according to said binary variables) 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.

- SMF improvement using Subject’s Impact Questionnaire answers will be summarized using descriptive statistics by study visit for each study arm. Shift from baseline will be evaluated and tabulated in the same manner.

7. RELATED DOCUMENTS (OPTIONAL)

RZL-012_PK SMFC_protocol 1.2, 26 July 2022_TC.docx

8. RELATED FORMS (OPTIONAL)

Not Applicable

9. REFERENCES

Not Applicable

10. APPENDICES

Not Applicable