Revision History

Revision	Revision Date	Reason for Revision/Change Request	Revised By
1.0	14-March-2018	Original Release	Daniel Manas, DMS
2.0	14-Nov-2018	Updated version	Daniel Manas, DMS

Final Statistical Analysis Plan

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

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SIGNATURES PAGE

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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
CDC	Center for Disease Control
cGMP	Current Good Manufacturing Practices
CI	Confidence Interval
CK-MM	Creatine Kinase - Muscle
C_{max}	Maximum observed concentration
CNS	Clinically not significant
CRF	Case Report Form
CPK	Creatine phosphokinase
CRP	C-reactive protein

CS	Clinically significant
CTC	Common terminology criteria
CTCAE	Common Terminology Criteria for Adverse Events
DICOM	Digital Imaging and Communications in Medicine
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
EF	Efficacy analysis set
ER	Emergency room
FDA	Food and Drug Administration
FFA	Free fatty acids
FIFO	First In First Out
FLASH	Fast-low-angle shot
FOB	Functional Observational Battery
GLP	Good Laboratory Practice
GTTP	Gamma-glutamyltransferase
HBV	Hepatitis B virus
HCRC	Hadassah Clinical Research Center
HCV	Hepatitis C virus
H&E	Hematoxylin and eosin stain
HDL	High-density lipoprotein
HED	Human equivalent dose
HIV	Human immunodeficiency virus
IC_{50}	Half maximal inhibitory concentration

ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonization Good Clinical Practice
IFN	Interferon
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LDH	Lactate dehydrogenase
LPL	Lipoprotein lipase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCP	Monocyte chemoattractant protein
MCV	Mean corpuscular volume
MD	Medical Doctor
MEDDRA	Medical Dictionary for Regulatory Activities
MPV	Mean platelet volume
MRI	Magnetic Resonance Imaging
NHANES	National Health and Nutrition Examination Survey
NOAEL	No observed adverse effect level
NSAIDs	Non Steroid Anti-Inflammatory Drugs
PI	Principal Investigator
PK	Pharmacokinetics
PKA	PK Analysis set
PT	Prothrombin time

PTT	Partial thromboplastin time
QA	Quality Assurance
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
TBD	To be determined
TC	Total Cholesterol
TG	Triglycerides
TGF	Transforming growth factor
T_{max}	Time of maximum observed sample concentration
TNF	Tumor necrosis factor
UCP1	Uncoupling protein 1
ULN	Upper limit of normal
US/USA	United States/United States of America

WAT	White adipose tissue
WBC	White blood cells
WHO	World health organization
WHR	Waist to hip ratio

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-P2aUS-001.4

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)	Daniel Manas	Senior Biostatistician & SAS Programmer
Statistical Report and listing appendix	Daniel Manas	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'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 final version V1.4, dated 4 March, 2018.

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 purpose of this study is to test safety and efficacy of a new chemical entity, RZL-012, in converting WAT into a thermogenic tissue and reducing fat-mass in overweight and obese males

5.2.2 RZL-012 investigational drug is intended for a single dose in multiple injections into the subcutaneous fat. The injection dosing regimen and technique is crucial for the therapy safety and efficacy. The RZL-012 drug is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 250 mg/4.8 mL RZL-012 in formulation F12. The vehicle is a ready to use liquid to be injected to the subcutaneous fat, supplied in a 1 vial kit. 1 vial contains 4.8 mL of formulation F12.

5.3 Study Objectives and Endpoints

5.3.1 Primary Objectives:

5.3.2 Evaluation of the overall safety and preliminary efficacy of RZL-012 after injection into the subcutaneous fat.

5.3.3 Primary Endpoints

5.3.4 Safety: The main objective is the evaluation of the overall safety of RZL-012 injection into the subcutaneous fat. Therefore, the primary endpoint will be the incidence of intolerable side effects and all adverse events of RZL-012 injection into the subcutaneous fat. The dose escalation scheme will be stopped if at any dose cohort, 2 patients will experience intolerable side effects.

5.3.5 Efficacy: The primary endpoint for efficacy is a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site. This was monitored by sensitive (± 0.1 °C) Infra-Red thermal camera. A thermogenic effect is defined by an increase of 1 °C in the injected site when compared to the surroundings and/or the non-injected site, apparent at least 28 days after injection and non-related to inflammatory response as determined by inflammatory cytokines. The primary efficacy evaluation will be supported by results from secondary endpoints, including MRI, biopsy and biomarkers

5.3.6 Secondary Objectives:

5.3.7 Determination of RZL-012 pharmacodynamics and pharmacokinetics. Evaluation of the existence of a thermogenic effect and the extent, duration and tissue associated changes of the thermogenic response to RZL-012, via minimal invasive means (injected-site thermogenesis imaging, Magnetic Resonance Imaging (MRI) and biopsy) after subcutaneous injection into fatty tissue below the skin.

5.3.8 Secondary Endpoints

5.3.9 Duration of the thermogenic effect, defined as a net-delta ≥ 1

5.3.10 Local reduction in fat mass as determined by MRI.

5.3.11 Clinical laboratory changes from baseline including improvement in fasting blood glucose and lipid profile.

5.3.12 Establishing pharmacokinetic profile for RZL-012.

5.3.13 Anthropometric changes from baseline, including body weight change.

5.3.14 Elucidation of the histological changes account for the thermogenic effect by biopsy of the injection site.

5.3.15 Change from baseline in inflammatory markers and cytokines.

5.4 Overall study design and plan

5.4.1 Study Design

5.4.2 This is a consecutive 4 cohort, dose escalation placebo-controlled clinical trial in overweight and obese subjects. All cohorts will be comprised of 6 active (RZL-012) and 2 placebo subjects.

5.4.3 Within each cohort, dosing of the first 3 subjects will progress consecutively from one individual to the other at 7-day intervals. For additional precaution, the first 3 subjects will be forced randomized into 2 active and 1 control. This study design will allow the physicians to monitor safety in a two subjects at each dose, nevertheless the blindness will remain intact. The remaining subjects in a cohort will be randomized to either active treatment or placebo in a ratio determined by the number of subjects targeted for each cohort. Dosing of the next subjects will be in couples and the last subjects will be in a triplet.

5.4.4 Schedule of Assessments

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Signed informed consent	X										
Medical history	X		X								

Study Procedure	Screening Day 1	Screening Day 2	Clinic Admission	Baseline (Treatment)	Visit Schedule (Days 1 to 28)						Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Complete physical exam	X									X	
Serology assays (HBV, HCV, HIV)	X										
Fasting glucose	X		X								
Fasting glucose, insulin, leptin and lipid profile (including FFA)			X							X	Every 28 days
Inflammatory markers and Cytokines - In subject of the 2nd, 3rd and 4th cohorts [b]			X				X	X	X	X	

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Photography of site of injection and contralateral	X				X		X	X	X	X	Every 28 days
MRI section around the umbilicus		X								X	
MRI section around the umbilicus – for cohort 2											On Day 56

Study Procedure	Screening Day 1	Screening Day 2	Clinic Admission	Baseline (Treatment)	Visit Schedule (Days 1 to 28)						Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
MRI section around the umbilicus – for 3rd and 4th cohort or in cohort 2 if 2 subject experience intolerable side effects in cohort 3)											Every 28 days
Anthropometric measurements: (weight, height) BMI, (waist & hip circumference) WHR	X	X	X							X	Every 28 days
Weight – by the subjects at home –							X	X	X		On weeks when

Study Procedure	Screening Day 1	Screening Day 2	Clinic Admission	Baseline (Treatment)	Visit Schedule (Days 1 to 28)						Follow-up Schedule for the highest dose cohorts [1] (Days 29 - 168)
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
morning(8-12hr overnight fast) and evening											not visiting the site
Urine Drug Screen	X		X								
Infra-Red thermal imaging of the injected site	X		X		X		X	X	X	X	On Day 56

Study Procedure	Screening Day 1	Screening Day 2	Clinic Admission	Baseline (Treatment)	Visit Schedule (Days 1 to 28)						Follow-up Schedule for the highest dose cohorts [l] (Days 29 - 168)
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Infra-Red thermal imaging of the injected site - for 3rd and 4th cohort or in cohort 2 if 2 subjects experience intolerable side effects will in cohort 3)[k]											Every 28 days
Serum Chemistry, Hematology [c]	X		X		X	X	X	X		X	
Histamine levels[d]			X		X	X		X			
Urinalysis	X							X		X	
Pharmacokinetics [f]				Pre [e] X post [e]	X						

Study Procedure	**Screening Day 1**	**Screening Day 2**	**Clinic Admission**	**Baseline (Treatment)**	**Visit Schedule (Days 1 to 28)**						**Follow-up Schedule for the highest dose cohorts [l] (Days 29 - 168)**
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Draize score at the injected site [g]	X			Pre [e] X post [e]	X		X	X	X	X	Every 28 days
Vital signs [h]	X			Pre [e] X post [e]	X		X	X	X	X	
Injection of RZL-012				X							
ECG [i]	X			X post [e]	X			X		X	
Pulse rate [j]				Pre [e] X post [e]	X						
Adverse event assessment					X----------→						Every 28 days
Adverse event assessment by phone for cohorts 1 and 2											On Day 84 and 112

Study Procedure	Screening Day 1	Screening Day 2	Clinic Admission	Baseline (Treatment)	Visit Schedule (Days 1 to 28)						Follow-up Schedule for the highest dose cohorts [l] (Days 29 - 168)
Study Day[a]	**Day[a]-(-28) through Day (-7)**	**Day[a]-(-14) through Day (-2)**	**Day (-1)**	**Day [a] 0**	**Day 1**	**Day 3**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 56, 84, 112, 140, 168**
Subjects diary recording weight							X	X	X		On weeks when not visiting the site
Biopsy – In subject of cohort 3 (or in cohort 2 if 2 subjects experience intolerable side effects in cohort 3)[k,l]											On Day 56

a. Study day is based on Day 0 defined as the day of RZL-012 injection.

b. Inflammatory markers and cytokines from the 2nd, 3rd and 4th cohorts (on 6 RZL-012 treated and 2 placebo treated subjects in each cohort)**: CRP,** Adiponectin, CD-163, Interleukin [IL]-1β, IL-4, IL-6, IL-10, IL12p70, IL-13, IL-23, Tumor necrosis factor [TNF] α and TGFβ1.

c. CBC, coagulation, serum chemistry analysis, renal and liver function , urinalysis, CPK, amylase measurement: before injection,14d and 28d following injection

d. Histamine blood level measurement: clinical admission, following drug injection (24h ± 2h), 3d and 14d following injection

e. Pre/post – refers to before/after injection respectively

f. Pharmacokinetics at the given time points: 0, 30, 60 min, 2h, 3h, 4h, 6h, 8h, 12h, 16h, 24h, 30h in subjects from the 1st, 2nd and 3rd cohorts. Pharmacokinetics will not be conducted in the fourth cohort as the injected dose is divided in 2 clusters 2 weeks apart.

g. Draize score evaluation: before injection, 2h, 24h and 7d,14d,21d and 28d following injection
h. Vital signs measurement: before injection, 2h, 24h and 7d,14d,21d and 28d following injection
i. ECG is to be performed in triplicate for all measurements in given time point: 4h, 12h, 24h, Day 14 and 28 following injection
j. Pulse rate measurements at given time points: 1h, 2h, 4h, 8h, 12h, 24h following injection in the opposite hand of blood sampling
k. For 3 subjects of cohort 3 (in cohort 2 if 2 subjects experience intolerable side effects in cohort 3) - if thermogenesis is evident by thermal camera by Day 56, biopsy from the injected for histology and BAT characterization**.**
l. For subjects from the 3rd (or in cohort 2 if 2 subjects will experience intolerable side effects within the 3rd cohort) and 4th cohort

5.4.5 Randomization, Blinding and Un-blinding

5.4.6 Subjects will be randomized to each study group, i.e., investigational therapy or control, left side injection or right side injection according to a predefined randomization scheme. 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

5.4.7 Masking will be used to blind the Investigator regarding randomization, i.e., assignment to study group will be disclosed only after subject eligibility is confirmed and immediately before treatment initiation. The pharmacist will be unmasked and will be responsible to fill the syringes for injection.

5.5 Selection of study population

5.5.1 Study Population

5.5.2 Male subjects

5.5.3 Age 20 - 60 years old

5.5.4 The study population include subjects who are obese by Body Mass Index (BMI) definition ($27.5 < BMI \leq 34.9$)

5.5.5 Rationale Sample Size Calculation

5.5.6 The planned sample size is 32 subjects (8 in each cohort). 6 subjects per dose group paradigm with the addition of a 2 subjects per control group for all doses. A maximum of 32 evaluable subjects will be included in the study (24 in the RZL-012 treatment arm and 8 in the placebo arm) and followed for as long as 3 months in the 2 lowest dose cohorts, and in the 2 highest dose cohorts for up to 5 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 Spaulding Clinical.

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

5.6.10 Protocol Violations and Deviations

5.6.11 Departures from the protocol should be avoided unless required for the safety of the subject. Protocol deviations and, if possible, the reason for occurrence will be documented by the study monitor and included in the final clinical study report.

5.6.12 The Investigator must report any protocol deviation to the Sponsor and, if required, to the IRB/IEC in accordance with local regulations, within reasonable time. All violations and deviations must be recorded in the study site's electronic system and signed by the Investigator (or designee).

5.7 Subject Population for analyses

5.7.1 The safety analysis set (SA) will consist of all enrolled subjects who received the study treatment, either RZL-012 or placebo (exposed population), including subjects prematurely withdrawn. All enrolled subjects receiving at least one study drug injection are considered evaluable for the SA set.

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

5.7.3 The efficacy analysis set (EF) will consist of all subjects from the SA analysis set without any major protocol violations measured at baseline

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

5.7.5 The PK analysis set will consist of all subjects with no major deviations related to study drug administration (e.g., incomplete injection of study drug).

5.7.6 The PK analysis set will serve as the principal data analysis set for the PK analysis

5.8 Statistical Analysis

5.8.1 General

5.8.2 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. For continuous variables summary tables will be provided giving sample size, arithmetic mean, standard deviation, standard error, coefficient of variation (CV%), median, minimum and maximum of variables, and 95% confidence intervals of means.

5.8.3 The data is analyzed using the SAS ® version 9.3 or higher (SAS Institute, Cary North Carolina). Analyses presented in the clinical report but not mentioned in the SAP are unplanned or ad-hoc analyses.

5.8.4 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.

5.8.5 Derived Data

5.8.6 Definition of baseline

5.8.7 Baseline is defined as the last non-missing value prior to the patient start of treatment (screening or baseline visit).

5.8.8 End of Study

5.8.9 The end-of-study visit is defined as Day 168.

5.8.10 Disposition of subjects (Table 14.1-1 – 14.1.2)

5.8.11 The number of subjects that are randomized into the study, the number of subjects in the Safety, efficacy analysis set, and PK populations, and the number of study completers will be presented.

5.8.12 The reasons for early termination/ withdrawal will be summarized.

5.8.13 Demographic and Baseline data (Tables 14.1-3 -14.1-4)

5.8.14 Baseline and demographic data will be summarized in appropriate tables using the Safety population. The data includes demographic characteristics (age and gender) and medical history.

5.8.15 Efficacy Analysis

5.8.1 The primary endpoint for efficacy is a significant thermogenesis at the injected site compared with the contra-lateral, non-injected site.

5.8.2 The average temperature will be presented in a tabular form by visit, side (treated / not treated) and treatment received (RZL-012 / placebo) by cohort and overall. Difference between the sides (treated – not treated) will be presented in a tabular form by visit treatment along with the change from baseline (net-delta) in these differences by cohort and overall.

5.8.3 Kruskal-Wallis will be used to compare the net-delta between the study arms for the relevant cohorts and visits.

5.8.4 The number and percent of subjects with a thermogenic effect, defined as a net-delta ≥ 1, will be presented by cohort and visit for the subjects in the active arm. The duration of the thermogenic effect after the Day 28 visit, for subjects in the active arm with thermogenic effect at the Day 28 visit will be presented.

5.8.5 Subcutaneous Fat Mass (SFM) ratio (treated sites / control sites) averaged over the MRI slices will be presented in tabular form by visit, treatment and cohort. The change from baseline in this ratio (in % from the ratio at baseline) will be presented in the same manner, and compared between the treatment arms with Kruskal-Wallis test.

5.8.6 Changes from baseline in fasting blood glucose, lipid profile, anthropometric changes, inflammatory markers and cytokines will be presented by visit, treatment, and cohort.

5.8.7 Histology results will be presented in tabular form by treatment for relevant subjects.

5.8.8 Safety analysis

5.8.9 Safety data will be summarized for the Safety population.

5.8.10 Adverse events will be coded according to coding dictionaries (the most updated version of MedDRA) and presented in tables by System Organ Class (SOC) and Preferred Term (PT) and by treatment group.

5.8.11 The incidence of AEs, as well as the intensity and relationship to study drug will be summarized by treatment group.

5.8.12 The incidence of all adverse events will be presented by treatment overall and by cohort along with two sided 95% exact binomial Confidence Interval (CI).

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

5.8.14 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.

5.8.15 Interim Analysis

5.8.16 An interim analysis is planned at the end of each cohort for evaluation of efficacy. For this purpose, a data lock (except for externally collected data such as PK) will be implemented after each cohort is completed. Upon lack of trends in efficacy due to effect size, the Sponsor will consider study termination

6. RELATED DOCUMENTS (OPTIONAL)

6.1 Study Protocol: RZL-012-P2aUS-001.4_track changes 04 Mrch 2018

6.2 Randomization plan: RZL-012-P2aUS random plan final version 1.0 01-08-2017.pdf

7. RELATED FORMS (OPTIONAL)

Not Applicable

8. REFERENCES

Not Applicable

9. APPENDICES (OPTIONAL)

9.1 APPENDIX I: TABLE SHELLS

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