Statistical Analysis Plan (SAP)

19RNHB

Protocol Title:	A randomized, double-blind, comparator-controlled, cross-over study to investigate the safety and efficacy of RiaGev™ in healthy adults
Protocol Number:	19RNHB
Protocol Version:	2.0; October 7, 2019
SAP Date:	June 24, 2020
Version:	1.0
Study Design:	Randomized, double-blind, comparator-controlled, cross-over study
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Signatures

I have read and approved of this statistical analysis plan for use in the study.

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1. Overview

1.1 Introduction

Nicotinamide adenine dinucleotide (NAD+) is one of the essential cofactors required for the proper function of living cells, and depletion in NAD has been correlated to ageing individuals as NAD is associated with oxidative stress and energy production (1). Per the Population Reference Bureau (PRB), it is estimated that by the year 2060, the number of Americans over the age of 65 will double to over 98 million (2). As well, over the years, there has been a continuous rise in obesity within older Americans, reaching 44% for women and 36% for men in the age range of 65-74 (2). One of the most common chronic diseases that are accompanied by ageing and obesity is diabetes. In 2016 the WHO reported that approximately 1.6 million deaths were attributed to diabetes. Half of these individuals had high blood glucose before the age of 70 (3). Hence it is crucial to actively control blood glucose and oxidative stress during one's midlife stage.

The investigational product RiaGev™ is the first and only commercially available product that contains Bioenergy Ribose® and vitamin B3 (4). It increases NAD+ in the body efficiently to promote healthy mitochondria, active immunity and cholesterol reduction. As a result, D-ribose is essential for healthy ageing (4).

Bioenergy Ribose® is a 5-carbon carbohydrate ($C_5H_{10}O_5$) called D-ribose designated as a Generally Recognized as Safe (GRAS) substance by the US Food and Drug Administration (FDA) (5). It is produced via the pentose phosphate pathway (PPP), which is fundamental for adenosine triphosphate (ATP) production (6). The PPP is a rate-limiting step that makes use of a short supply enzyme called glucose-6-phosphate dehydrogenase (G-6-PDH) (6). Supplementation of D-ribose can bypass the PPP and directly contribute to ATP production (6). In addition, to its function for ATP production D-ribose is a critical element of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and acetyl coenzyme A (6). Provided there is a reduction in ATP production; ageing is frequently due to a decline in mitochondria function. Hence, cell function and integrity are compromised, leading to chronic cardiovascular conditions and fatigue (6). With active D-ribose supplementation, improvements have been noted in several pathological conditions such as chronic fatigue syndrome, fibromyalgia, and myocardial dysfunction (6). Furthermore, D-ribose demonstrated improvements in athletic performances by recovering ATP levels and repairing cellular damage (6).

Vitamin B3 is an essential water-soluble vitamin known as either niacin, nicotinic acid, or nicotinamide. It is found in foods such as chicken, beef, fish, nuts, legumes, and grains (7). Also, vitamin B3 can be obtained from conversions of tryptophan in the body. Therefore, foods with tryptophan such as milk, eggs, meat and fish are another great source of vitamin B3 (7,8). Once vitamin B3 is consumed, it is converted into two different active forms called NAD+ or nicotinamide adenine dinucleotide phosphate (NADP) (7,8). NAD+ and NADP are essential for various metabolic redox processes with oxidized or reduced substrates. Cellular functions like genome integrity, gene expression, and cellular communication are carried out by NAD+ required enzymes (7). These required enzymes are also crucial for the production of ATP via energy transfer from carbohydrates, fats, and proteins (7). NADP is involved in fewer reactions than NAD+ such as cholesterol and fatty acid synthesis along with antioxidation (7). Lack of NAD+ has

been associated with a variety of ageing related conditions such as metabolic syndrome, cardiovascular health, and cancer (1).

This current randomized, double-blind, comparator-controlled, cross over study will investigate the efficacy and safety of RiaGev™ via evaluation of NAD+, glucose and insulin, in healthy adults of ages 35-65.

1.2 Study Objective

The objective of this study is to evaluate the safety and efficacy of RiaGev™ in healthy adults.

1.3 Primary Outcome

The primary endpoint is the change in whole blood NAD+ levels from baseline to day 8 when supplemented with RiaGev™ or comparator.

1.4 Secondary Outcomes

1. The change in serum glucose and insulin as assessed by an Oral Glucose Tolerance Test (OGTT) at t=0, 15m, 30, 45m, 60m, 90m and 2h after a 7-day supplementation with either RiaGev™ or comparator.
2. The change in serum Glutathione/Glutathione disulfide (GSH/GSSG) ratio after a 7-day supplementation with either RiaGev™ or comparator
3. The change in serum adenosine triphosphate/ adenosine monophosphate (ATP/AMP) ratio after a 7-day supplementation with either RiaGev™ or comparator
4. The change in salivary cortisol after a 7-day supplementation with either RiaGev™ or comparator
5. The change in Checklist Individual Strength (CIS) Questionnaire outcome after a 7-day supplementation with either RiaGev™ or comparator.

1.5 Safety Outcomes

1. Incidence of pre-emergent and post-emergent adverse events when supplemented
2. Vital signs (blood pressure (BP) and heart rate (HR)) when supplemented
3. Clinical chemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, electrolytes (Na, K, Cl), fasting glucose and estimated glomerular filtration rate (eGFR))
4. Hematology (white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, RBC indices (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW)

1.6 Inclusion Criteria

1. Healthy male and females between the ages of 35 and 65 years of age, inclusive
2. BMI between 18.5 to 29.9 kg/m^2, inclusive

3. Female participant is not of child-bearing potential, defined as females who have undergone a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, bilateral tubal ligation, complete endometrial ablation) or have been post-menopausal (natural or surgically) for at least 1 year prior to screening

   Or,

   Females of child-bearing potential must have a negative urine pregnancy test at screening and baseline and agree to use a medically approved method of birth control for the duration of the study. All hormonal birth control must have been in use for a minimum of three months. Acceptable methods of birth control include:
   - Hormonal contraceptives including oral contraceptives, hormone birth control patch (Ortho Evra), vaginal contraceptive ring (NuvaRing), injectable contraceptives (Depo-Provera, Lunelle), or hormone implant (Norplant System)
   - Double-barrier method
   - Intrauterine devices
   - Non-heterosexual lifestyle or agrees to use contraception if planning on changing to heterosexual partner(s)
   - Vasectomy of partner at least 6 months prior to screening
4. Healthy as determined by laboratory results, medical history, physical exam, and EKG
5. Agrees to avoid supplementation with tryptophan and vitamin B3 or its derivatives (niacin, nicotinic acid, niacinamide) one week prior to randomization and during the study
6. Ability to complete maximal and submaximal exercise tests
7. Agrees to maintain current diet and activity level throughout the study
8. Agrees to comply to all study procedures
9. Has given voluntary, written, informed consent to participate in the study
10. Self-reported good sleeper at screening. Have a regular sleep cycle with a bedtime between the approximate hours of 9:00pm and 12:00am and regularly receive between 7-9 hours of sleep, and agrees to maintain this sleep schedule throughout the study

1.7 Exclusion Criteria

11. Women who are pregnant, breast feeding, or planning to become pregnant during the trial
12. Allergy or sensitivity to investigational product's ingredients or standard meal provided
13. Current or ex-smokers within the past year
14. Major surgery within the past 3 months which may impact the study outcomes to be assessed by the QI.
15. Untreated/unresolved/uncontrolled cardiovascular disease. Participants with no significant cardiovascular event in the past 1 year and on stable medication may be included after assessment by the QI on a case by case basis
1. Self-reported current or pre-existing thyroid condition. Treatment on a stable dose medication for over 3 months will be reviewed on a case-by-case basis by the QI

2. Current or history of hypertension.
3. Type I or Type II diabetes
4. Cancer, except skin cancers completely excised with no chemotherapy or radiation with a follow up that is negative. Volunteers with cancer in full remission for more than five years after diagnosis are acceptable
5. Self-reported of any autoimmune disease or immune-compromised
6. Self-reported by subjects of being HIV or Hepatitis B/C positive
7. History or currently with kidney and liver diseases assessed by QI on a case by case basis, with the exception of history of kidney stones symptom free for 1 year
8. Known medical or psychological condition that, in the qualified investigator's opinion, could interfere with study participation
9. Significant gastrointestinal disease (examples include but are not limited to Celiac disease and inflammatory bowel disease)
10. Self-reported of bleeding disorders.
11. Current diagnosis of gout within past three months as per the QI's assessment
12. Clinically significant abnormal laboratory results at screening as assessed by QI
13. Current use of prescribed medications or over the counter supplements that may interfere with the IP assessed by QI (See Section 7.3)
14. Alcohol consumption of >2 standard drinks/day or >14 drinks/week
15. Alcohol or drug abuse within the past 12 months
16. Use of medical marijuana
17. Frequent use of recreational drugs within 6 months of baseline assessed as per QI
18. Planned blood donation during or within 30 days following conclusion of clinical trial
19. Participation in other clinical research trials 30 days prior to baseline
20. Participants that are cognitively impaired and/or who are unable to give informed consent
21. Any other active or unstable medical condition, that, in the opinion of the QI, may adversely affect the participant's ability to complete the study or its measures or pose significant risk to the participant.

1.8 Study Design, Visit Breakdown and Schedule of Assessment

This is a randomized, double-blind, comparator-controlled, crossover study to evaluate safety and efficacy conducted at Prism Clinical Research Clinic, Saint Paul, MN, USA, a KGK Science Inc. partner.

A total of 18 participants were enrolled in the study. The allocation of participants is provided in **Table 1**. The schedule of visits is presented in **Figure 1**. The schedule of assessments is described in **Table 2**.

Table 1. Allocation of participants

Study Arm	Number of Participants
RiaGev™ →Comparator	N = 9
Comparator→ RiaGev™	N = 9
Total	N = 18

Figure 1. Study design

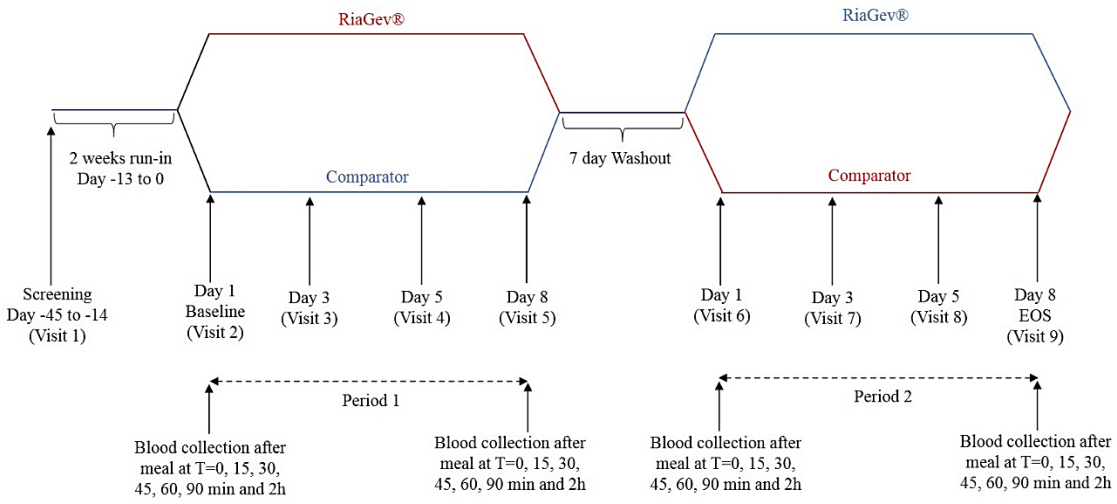

Table 2. The schedule of assessments

Procedures/assessments	Visit 1 Screen	Visit 2 Day 1 (+1 Day)	Visit 3 Day 3 (+1 Day)	Visit 4 Day 5 (+1 Day)	Visit 5 Day 8 (+1 Day)	Visit 6 Day 1 (+1 Day)	Visit 7 Day 3 (+1 Day)	Visit 8 Day 5 (+1 Day)	Visit 9 Day 8 (+1 Day)
Informed consent	X								
Review inclusion/exclusion criteria	X	X							
Review medical history	X								
Review concomitant therapies	X	X	X	X	X	X	X	X	X
Vitals: Height*, weight, heart rate, blood pressure ***Height will only be measured at Visit 1***	X	X	X	X	X	X	X	X	X
Urine pregnancy test	X	X							
Electrocardiogram (EKG)	x								
Physical examination	X	X							X

Procedures/assessments	Visit 1 Screen	Visit 2 Day 1 (+1 Day)	Visit 3 Day 3 (+1 Day)	Visit 4 Day 5 (+1 Day)	Visit 5 Day 8 (+1 Day)		Visit 6 Day 1 (+1 Day)	Visit 7 Day 3 (+1 Day)	Visit 8 Day 5 (+1 Day)	Visit 9 Day 8 (+1 Day)
Randomization		X								
CBC, electrolytes (Na, K, Cl), HbA1c*, fasting glucose, eGFR, creatinine, AST, ALT, and total bilirubin **HbA1c will only be measured at Visit 1*	X				X		X			X
Maximum heart rate (HR_{max}) treadmill test	X									
Skin fluoroscopy for NADH analysis (optional)		X			X		X			X
Blood Collection for NAD+ analysis		X	X	X	X		X	X	X	X
Blood Collection for GSH/GSSG and ATP/AMP analyses		X			X		X			X
OGTT: glucose and insulin T= 0, 15m, 30m, 45m, 60m, 90m, 2h		X			X		X			X
Questionnaire		X	X	X	X		X	X	X	X
Treadmill Exercise protocol		X			X		X			X
Salivary Collection Kit Dispensed	X	X	X	X	X		X	X	X	
Salivary Collection Kit Returned		X	X	X	X		X	X	X	X
Food Records Dispensed	X	X	X	X	X		X	X	X	
Food Records Collected		X	X	X	X		X	X	X	X
IP Dispensed		X	X	X			X	X	X	
IP Returned			X	X	X			X	X	X
Subject Diary Dispensed	X	X	X	X	X		X	X	X	
Subject Diary Returned		X	X	X	X		X	X	X	X
Standardized Meal		X			X		X			X
Compliance Calculated			X	X	X			X	X	X
Adverse Events	X	X	X	X	X		X	X	X	X

1.9 Study Populations

A total of three populations are defined for all summaries and analyses. Subjects who have satisfied the population criteria will be classified in the designated population.

Intent-to-Treat (ITT) Population

The ITT population consists of all subjects who received either product, and on whom any post-randomization efficacy information is available. The ITT population will be used to present all the effectiveness information according to the treatment to which subjects were randomised.

Per Protocol (PP) Population

The PP Population consists of all subjects who consumed at least 80% of treatment or placebo doses, did not have any major protocol violations and completed all study visits and procedures connected with measurement of the primary variable.

Safety Population

Safety Population consists of all subjects who received any amount of either product, and on whom any post-randomization safety information is available.

2. Statistical Methods

2.1 General Approach

The primary and secondary endpoints will be analysed for both ITT and PP population. Safety parameters will be analysed for Safety population. All data will be summarised by study group, visit and/or study week as specified in the study objectives.

For nominal variables, counts and percentages will be presented. The denominator for each percentage will be the number of participants within the study group at that visit unless otherwise specified.

For interval variables, the arithmetic mean, standard deviation, median and min-max range will be presented to two decimal places. This will be accompanied by the number of participants included in the analysis for that time point.

Changes in interval endpoints from pre-supplementation will be calculated as:

$$Change\ to\ V_i = Value\ at\ V_i - Value\ at\ V_{pre\text{-}supplementation}$$

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001. P-values less than or equal to 0.05 will be considered statistically significant. All analyses will be performed using R Statistical Software version 3.6.1 (R Core Team, 2019) for Microsoft Windows.

2.1.1 Background and Demographic Characteristics

Demographic and biometric information and vital signs at screening/baseline will be presented

for the ITT and PP populations. This will include the following:

- Age (years)
- Gender (male/female)
- Ethnicity (African/African American/Central American/East Asian/Eastern European White/Hispanic or Latino/Middle Eastern/Native American/South Asian/South American/South Asian/South American/South East Asian/Western European White)
- Weight (kg)
- BMI (kg/m^2)
- Systolic Blood Pressure (mm Hg)
- Diastolic Blood Pressure (mm Hg)
- Heart Rate (bpm)

2.1.2 Treatment Exposure and Compliance

Number of dosage units taken will be assessed by counting the number of returned unused test product(s) at each visit and subtracting this from the total number of dosage units dispensed. Compliance will be calculated by determining the number of dosage units taken divided by the number of dosage units expected to have been taken, multiplied by 100.

$$\frac{\textit{number of dosage units taken}}{\textit{number of dosage units expected to have been taken}} \times 100\%$$

Possible differences in compliance between the study groups at the end of each treatment will be assessed using a Mixed Model. The model will include treatment, sequence and period as fixed effects and subject as a random effect.

2.1.3 Premature Discontinuation/Early termination

For each premature discontinuation, the following parameters will be listed: subject number, sequence, and the reason of premature discontinuation.

2.1.4 Protocol Deviations

Protocol deviations will be listed with subject number, date and description of protocol deviation in the final report.

2.2 Effectiveness/Efficacy analysis

2.2.1 Primary Outcome:

The primary outcome is the change in whole blood NAD+ levels from baseline to day 8 when supplemented with RiaGev™ or comparator.

The primary null hypothesis is as follows:

H_0: There is no significant difference in mean change in NAD+ level from pre-supplementation to post-supplementation, between subjects taking RiaGev™ or comparator.

Possible differences before exercise from day 1 to days 3, 5 and 8 between the study groups will be assessed using repeated-measures mixed ANCOVA. The model will include treatment, visit number, sequence and period as fixed effects and subject as a random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

Possible differences at after exercise from day 1 to day 8 between the study groups will be assessed using repeated-measures mixed ANCOVA. The model will include treatment, visit number, sequence and period as fixed effects and subject as a random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

2.2.2 Secondary Outcomes

1. The change in serum glucose and insulin as assessed by an Oral Glucose Tolerance Test (OGTT) at t=0, 15m, 30, 45m, 60m, 90m and 2h after a 7-day supplementation with either RiaGev™ or comparator.

The change in serum glucose and insulin will be represented as change in mean concentrations at each time point. Assessment of change in mean concentrations for each analyte will be conducted using repeated-measures mixed ANOVA. The model will include treatment, time, sequence and period as fixed effects and subject as the random effect. Between group p-values will be obtained from this model, while within group p-values (from day 1 to day 8) will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate. An incremental area under the curve (iAUC) will be calculated for each group and compared between groups using mixed ANOVA, with study group, sequence and period as fixed effects and subject as the random effect.

2. The change in serum Glutathione/Glutathione disulfide (GSH/GSSG) ratio after a 7-day supplementation with either RiaGev™ or comparator

Assessment of the change in the ratio from day 1 to day 8 will be conducted using repeated-measures mixed ANCOVA. The model will include treatment, sequence and period as fixed effects and subject as the random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

3. The change in serum adenosine triphosphate/ adenosine monophosphate (ATP/AMP) ratio after a 7-day supplementation with either RiaGev™ or comparator

Assessment of the change in the ratio from day 1 to day 8 will be conducted using repeated-measures mixed ANCOVA. The model will include treatment, sequence and period as fixed effects and subject as a random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

4. The change in salivary cortisol after a 7-day supplementation with either RiaGev™ or comparator

Assessment of the change in the level of salivary cortisol from day 1 to days 3, 5 and 8 will be conducted using repeated-measures mixed ANCOVA. The model will include treatment, visit number, sequence and period as fixed effects and subject as the random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

5. The change in Checklist Individual Strength (CIS) Questionnaire outcome after a 7-day supplementation with either RiaGev™ or comparator

The domains for this questionnaire are:

1. Subjective feeling of fatigue: sum of the scores for items 1, 4, 6, 9, 12, 14, 16, and 20
2. Concentration: sum of the scores for items 3, 8, 11, 13, and 19
3. Motivation: sum of the scores for items 2, 5, 15, and 18
4. Physical activity: sum of the scores for items 7, 10, and 17
5. Total: sum of the scores for the four sub-scales listed above

For item 2, 5, 6, 7, 8, 11, 12, 15, and 20, the score is 1 for “yes, that is true” and 7 for “no, that is not true”. For item 1, 3, 4, 9, 10, 13, 14, 16, 17, 18, and 19, the score is 7 for “yes, that is true” and 1 for “no, that is not true”.

Assessment of change in each CIS domain will be conducted using repeated-measures mixed ANCOVA. The model will include treatment, visit number, sequence and period as fixed effects and subject as the random effect. Between group p-values will be obtained from this model, while within group p-values will be obtained using paired t tests or Wilcoxon Signed Rank test as appropriate.

2.2.3 Exploratory & Subgroup Analyses

Exploratory and subgroup analyses may be performed using the same methodology as for primary and secondary outcomes.

2.3 Safety Analysis

2.3.1 Adverse Events

For adverse events, a descriptive analysis will be conducted. Adverse events will be presented in a frequency table by System Organ Class (SOC), Preferred Term (PT), Lower Level Term (LLT) and study group. Furthermore, the lower level term, intensity, relationship, action taken, and outcome will be reported for each adverse event. Lastly, a summary of adverse events that are possibly or probably related to the study product will be presented.

The proportion of at least one adverse event when taking RiaGev™ or comparator at pre-supplementation and post-supplementation will be assessed using a Chi Square or Fisher’s Exact test as appropriate.

2.3.2 Other Safety Variables

Clinically significant measurements for the variables listed below will be discussed as part of the final study report.

1. Vital signs (blood pressure (BP) and heart rate (HR))
2. clinical chemistry (alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, electrolytes (Na, K, Cl), fasting glucose and estimated glomerular filtration rate (eGFR))
3. hematology (white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, RBC indices (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW)

2.4 Statistical and Analytical Issues

2.4.1 Handling of Dropouts and Missing Data

Missing values in the intention-to-treat analysis will be imputed using the last available value ("last-observation-carried-forward" (LOCF)) or multiple imputation methods as appropriate. No imputation will be performed for missing values in the per protocol or the safety populations.

2.4.2 Outliers

Every outlier will be checked at data validation before unblinding the study. Interval variables will be checked by visual inspection using histograms, box-plots or scatter plots, and verified by referral back to source documents. If the values are not erroneous, they will be included in the analysis.

2.4.3 Site Effects

This is a single centre study, therefore there will be no controlling for site effects.

2.4.4 Assessment of Model Fit

Q-Q plots and histograms will be generated for the evaluation of normality of the residuals of mixed models. If the residuals are highly skewed, ranks, log or other transformation of the dependent variable will be performed.

2.4.5 Adjustments of Multiple Comparisons

Since there are only two study groups involved, there will be no pairwise comparisons requiring adjustment. There will be no adjustment for multiple outcomes.

3. Reference List

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4. Appendix

Table 3. Summary of outcomes and analysis methods

Outcome	Data type	Between groups analysis methods
Primary Outcome		
1. The change in whole blood NAD+ levels from baseline to day 8 when supplemented with RiaGev™ or comparator.	Interval	Repeated-measures mixed ANCOVA
Secondary Outcomes		
1. The change in serum glucose and insulin as assessed by an Oral Glucose Tolerance Test (OGTT) at t=0, 15m, 30, 45m, 60m, 90m and 2h after a 7-day supplementation with either RiaGev™ or comparator	Interval	Repeated-measures mixed ANOVA (change in concentrations); mixed ANOVA (iAUC)
2. The change in serum Glutathione/Glutathione disulfide (GSH/GSSG) ratio after a 7-day supplementation with either RiaGev™ or comparator	Interval	Repeated-measures mixed ANCOVA
3. The change in serum adenosine triphosphate/ adenosine monophosphate (ATP/AMP) ratio after a 7-day supplementation with either RiaGev™ or comparator	Interval	Repeated-measures mixed ANCOVA
4. The change in salivary cortisol after a 7-day supplementation with either RiaGev™ or comparator	Interval	Repeated-measures mixed ANCOVA
5. The change in Checklist Individual Strength (CIS) Questionnaire outcome after a 7-day supplementation with either RiaGev™ or comparator	Interval	Repeated-measures mixed ANCOVA
Safety Outcomes		
1. Proportion of participants experiencing at least one adverse event when taking RiaGev™ or comparator	Nominal	Chi Square or Fisher's Exact Test
2. The effect of supplementation with RiaGev™ or comparator on vital signs (blood pressure and heart rate) and anthropometrics (weight and BMI) from pre-supplementation to Day 7 post-supplementation a. blood pressure (BP) b. heart rate (HR)	 Interval Interval	*Not applicable*
3. The effect of supplementation with RiaGev™ or comparator on clinical chemistry from screening to end-of-study as assessed by a. alanine aminotransferase (ALT) b. aspartate aminotransferase (AST) c. total bilirubin d. creatinine e. sodium (Na)	 Interval Interval Interval Interval	*Not applicable*

Outcome	Data type	Between groups analysis methods
f. potassium (K) g. chloride (Cl) h. fasting glucose i. estimated glomerular filtration rate (eGFR)	Interval Interval Interval Interval Interval	
4. The effect of supplementation with RiaGev™ or comparator on hematology from screening to end-of-study as assessed by a. white blood cell (WBC) count b. neutrophils c. lymphocytes d. monocytes e. eosinophils f. basophils g. red blood cell (RBC) count h. hemoglobin i. hematocrit j. platelet count k. mean corpuscular volume (MCV) l. mean corpuscular hemoglobin (MCH) m. mean corpuscular hemoglobin concentration (MCHC) n. red cell distribution width (RDW)	 Interval Interval Interval Interval Interval Interval Interval Interval Interval Interval Interval Interval Interval Interval	*Not applicable*
Demographic Characteristics & Other Outcomes		
1. Age	Interval	*Not applicable*
2. Gender	Nominal	*Not applicable*
3. Ethnicity	Nominal	*Not applicable*
4. Overall Compliance	Interval	ANOVA
5. Food Records (calories, fat, sodium, carbohydrates, saturated fat, cholesterol, protein, fiber, sugars, potassium, Vitamins A, B6, B12, C, D and E, thiamin, riboflavin, niacin, folic acid, calcium, iron, magnesium, zinc, alcohol, folate and transfat	Interval	Repeated-measures mixed ANCOVA

Table 4. Checklist individual strength questionnaire

********* CIS20R *********
Checklist Individual Strength
University Hospital Nijmegen
Department of Medical Psychology

Instruction:
On the next page you find 20 statements. With these statements we wish to get an impression of how you have felt during the past two weeks. For example:

I feel relaxed

If you feel that this statement is not true at all, place a cross in the right box; like this:

I feel relaxed	**yes**, that is true	X							**no**, that is not true

If you feel that this statement is not true at all, place a cross in the right box; like this:

I feel relaxed	**yes**, that is true							X	**no**, that is not true

If you feel that this statement in not "yes, that is true", but also not "no, that is not true", place a cross in the box that is most in accordance with how you have felt.
For example, if you feel relaxed, but not very relaxed, place a cross in one of the boxes close to "yes, that is true": like this:

I feel relaxed	**yes**, that is true			X					**no**, that is not true

Do not skip any statement and place only one cross for each statement.

1. I feel tired	yes, that is true							no, that is not true
2. I feel very active	yes, that is true							no, that is not true
3. Thinking requires effort	yes, that is true							no, that is not true
4. Physically I feel exhausted	yes, that is true							no, that is not true
5. I feel like doing all kinds of nice things	yes, that is true							no, that is not true
6. I feel fit	yes, that is true							no, that is not true
7. I do quite a lot within a day	yes, that is true							no, that is not true
8. When I am doing something, I can concentrate quite well	yes, that is true							no, that is not true
9. I feel weak	yes, that is true							no, that is not true
10. I don't do much during the day	yes, that is true							no, that is not true
11. I can concentrate well	yes, that is true							no, that is not true
12. I feel rested	yes, that is true							no, that is not true
13. I have trouble concentrating	yes, that is true							no, that is not true
14. Physically I feel I am in a bad condition	yes, that is true							no, that is not true
15. I am full of plans	yes, that is true							no, that is not true
16. I get tired very quickly	yes, that is true							no, that is not true
17. I have a low output	yes, that is true							no, that is not true
18. I feel no desire to do anything	yes, that is true							no, that is not true
19. My thoughts easily wander	yes, that is true							no, that is not true
20. Physically I feel in a good shape	yes, that is true							no, that is not true

SCORING CIS20R
For the items: **2, 5, 6, 7, 8, 11, 12, 15, 20** is the scoring as follows:

yes, that is true	1	2	3	4	5	6	7	**no**, that is not true

For the items: **1, 3, 4, 9, 10, 13, 14, 16, 17, 18, 19** is the scoring as follows:

yes, that is true	7	6	5	4	3	2	1	**no**, that is not true

Subsequently **the four subscales** are calculated by summing the respective items

subscale 1: Subjective feeling of fatigue	items 1, 4, 6, 9, 12, 14, 16, 20
subscale 2: Concentration	items 3, 8, 11, 13, 19
subscale 3: Motivation	items 2, 5, 15, 18
subscale 4: Physical activity	items 7, 10, 17