Statistical Analysis Plan (SAP)

16GCHY

Protocol Title: A randomized, placebo-controlled, double-blind, parallel study to determine the effect of Farlong NotoGinseng™ (Farlong Ginseng Plus®) on cholesterol and blood pressure

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1. Overview

1.1 Study Goal

The objective of this study was to determine the effect of Farlong NotoGinseng™ (Farlong Ginseng Plus®) on cholesterol and blood pressure.

1.2 Study Design

This was a randomized, placebo-controlled, double-blind, parallel study with a 4-week therapeutic lifestyle change diet (TLC) run-in period and a 12-week supplementation period. The study was conducted at a single site at KGK Synergize Inc. in London, Ontario, Canada.

1.3 Study Timepoints

Subjects were expected to participate in the study for up to 84 days. Subjects attended the study at visit 1 (screening) for informed consent and at visit 2 (baseline) for confirmation of eligibility and randomization.

Participants were scheduled to be assessed at visit 1 (screening, day -56 to day -28), visit 2 (baseline, day 0), visit3 (day28), visit 4 (day 56), and visit 5 (end of study, day 84). The demographic information and medical history were recorded at visit 1. Details of the schedule of assessments are shown in Appendix table 1.

1.4 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.

- The **Safety Population** will consist of all participants who received any amount of either product, and on whom any post-randomization safety information is available.
- The **Intent-to-Treat (ITT) Population** will consist of all participants who received either product, and on whom any post-randomization efficacy information is available.
- The **Per Protocol (PP) Population** will consist of all participants who consumed at least 80% of supplement or placebo doses, do not have any major protocol violations and complete all study visits and procedures connected with measurement of the primary variable.

1.5 Primary Outcome

The difference in serum LDL-C from baseline to week 12 between Farlong NotoGinseng™ (Farlong Ginseng Plus®) and placebo after 12 weeks of supplementation

1.6 Secondary Outcomes

1. The difference in serum LDL-C from baseline to week 8 between Farlong Notoginseng and placebo
2. The difference in blood pressure from baseline to week 8 between Farlong Notoginseng and placebo

3. The difference in blood pressure from baseline to week 12 between Farlong Notoginseng and placebo
4. The difference in triglycerides from baseline to week 8 between Farlong Notoginseng and placebo
5. The difference in triglycerides from baseline to week 12 between Farlong Notoginseng and placebo
6. The difference in HDL-C from baseline to week 8 between Farlong Notoginseng and placebo
7. The difference in HDL-C from baseline to week 12 between Farlong Notoginseng and placebo
8. The difference in total cholesterol from baseline to week 8 between Farlong Notoginseng and placebo
9. The difference in total cholesterol from baseline to week 12 between Farlong Notoginseng and placebo
10. The difference in endothelial vasodilation, as measured by the EndoPAT, from baseline to week 8 between Farlong Notoginseng and placebo
11. The difference in endothelial vasodilation, as measured by the EndoPAT, from baseline to week 12 between Farlong Notoginseng and placebo

1.7 Safety Outcomes

1. Vital signs (heart rate) in the Farlong Notoginseng and placebo group
2. Weight and BMI in the Farlong Notoginseng and placebo group
3. Hematology (complete blood count (CBC)), Hb1Ac, electrolytes (Na, K, Cl, Ca), liver function (bilirubin, AST, ALT) and kidney function (creatinine) in the Farlong Notoginseng and placebo group
4. Incidence of adverse events in the Farlong Notoginseng and placebo over the course of the study

2. Statistical Evaluation

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 and/or visit as specified in the study objectives.

For continuous variables, the minimum and maximum, the arithmetic mean, median, and standard deviation will be presented to two decimal places. This will be accompanied by the number of subjects included in the analysis for that time point.

For categorical variables, counts and percentages will be used. The denominator for each percentage will be the number of subjects within the population study group unless otherwise specified.

Changes in continuous endpoints from screening/baseline will be calculated as:

$$\text{Change to } V_i = \text{Value at } V_i - \text{Value at } V_{\text{screening/baseline}}$$

All hypothesis tests will be carried out at the 5% (2-sided) significance level unless otherwise specified. P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001 in tables.

All analyses will be performed using R Statistical Package or SAS.

2.1.1 Demographic Characteristics

Demographic and biometric information and vital signs at screening will be presented for the ITT and PP populations. This will include the following:

1. Age (years)
2. Gender (male/female)
3. 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)
4. Weight (kg)
5. Systolic blood pressure (mmHg)
6. Diastolic blood pressure (mmHg)
7. Heart rate (bpm)

Age, weight, BMI, blood pressure, and heart rate will be described as continuous variables. Gender and ethnicity will be treated as categorical variables.

Possible differences at screening for continuous variables between two groups will be assessed by independent two-sample t-test, and Satterthwaite's correction will be conducted when the variances of the two groups are significantly different.

Possible differences for categorical variables between two groups will be assessed by the chi-square test or Fisher’s exact (2-tail) test, as appropriate.

2.1.2 Treatment Exposure and Compliance

Compliance will be calculated with the number of dosage units taken divided by the number of dosage units expected to have been taken multiplied by 100.

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

Compliance will be analysed as a continuous variable.

Possible differences for compliance between two groups at each visit and throughout the follow-up will be assessed by independent two-sample t-test, and Satterthwaite's correction will be conducted when the variances of the two groups are significantly different.

2.1.3 Premature Discontinuation

For each premature discontinuation, the following parameters will be listed: participant number and the reason for premature discontinuation.

2.1.4 Protocol Deviations

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

2.2 Efficacy analysis

An effectiveness analysis based on the intent-to-treat population and the per protocol population will be performed with the same statistical method. LDL-C, Blood pressure, triglycerides, HDL-C, total cholesterol, EndoPAT score will be assessed as continuous variables.

Possible differences at baseline between two groups will be assessed by independent two-sample t-test, and Satterthwaite's correction will be conducted when the variances of the two groups are significantly different.

2.2.1 Primary Variable:

The primary outcome variable is serum LDL-C.

The primary hypotheses of the change in serum LDL-C are as follows:

H_0: $\mu_a = \mu_b$

H_1: $\mu_a \neq \mu_b$

Where μ_a = mean change of LDL-C from baseline to week 12 in group A

μ_b = mean change of LDL-C from baseline to week 12 in group B

The null hypothesis will be assessed by Mixed Model for Repeated Measures. The model will include the change value of the outcome variable at each visit as a dependent variable, baseline value of the dependent variable as a covariate, and group, visit and group by visit as fix effects. Four covariance structures will be tested separately and the one that provided the smallest AIC will be selected. The tested covariance structures included Compound Symmetry (CS), Heterogeneous CS (CSH), first-order autoregressive [AR(1)], and heterogeneous autoregressive [ARH(1)]. P-values for between group comparisons and within-group changes from baseline will be obtained from the model.

2.2.2 Interim Analysis
There was no planned interim analysis in this study.

2.2.3 Secondary Variable
The following secondary variables will be assessed as the method of serum LDL-C described in section 2.2.1:

1. LDL-C
2. Blood pressure
3. Triglycerides
4. HDL-C
5. Total cholesterol
6. EndoPAT score

2.2.4 Exploratory and 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 Safety Variable
The available values at each visit will be described for the following safety variables:

1. Heart rate
2. Weight and BMI
3. Hematology (complete blood count (CBC)), Hb1Ac, electrolytes (Na, K, Cl, Ca), liver function (bilirubin, AST, ALT) and kidney function (creatinine)

Heart rate, weight, BMI, CBC, Hb1Ac, Na, K, Cl, Ca, bilirubin, AST, ALT, and creatinine will be treated as continuous variables.

2.3.2 Adverse Events
Adverse events (AEs) will be presented separately as the number and percentage of subjects for each system organ class, preferred term, and lower level term. Furthermore, the lower level term, intensity, relationship, action taken, and outcome will be reported for each adverse event. The difference of adverse event between two groups will be assessed with two-tailed Chi-square or Fisher's exact test as appropriate.

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 assessed for reasons and pattern for missingness and imputed with multiple imputation method as a sensitivity analysis. No imputation will be performed for missing values of the per protocol or the safety populations.

2.4.2 Outliers

Every outlier will be checked at data validation before unblinding the study. Continuous 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-site study. Therefore, site effect is not relevant.

2.4.4 Assessment of Model Fit

Q-Q plot and histogram will be generated for the evaluation of normality of the residuals of the model. If the residuals are highly skewed, ranks, log or other transformation of the dependent variable will be performed.

3. Appendix

Table 1. Schedule of Assessments

	Visit 1 Screening	Phone Call	Visit 2 Baseline Day 0	Visit 3 Day 28 Week 4	Visit 4 Day 56 Week 8	Visit 5 Day 84 Week 12
Informed consent	X					
Review inclusion/exclusion criteria	X		X			
Review medical history	X					
Review concomitant therapies	X		X	X	X	X
Height*, weight, heart rate, blood pressure (diastolic and systolic)	X		X	X	X	X
Urine pregnancy test	X					
Randomization			X			
Physical examination			X			
Framingham Risk Score Assessment	X					
Laboratory test: CBC, electrolytes (Na, K, Cl, Ca), HbA1c, creatinine, AST, ALT, bilirubin, hs-CRP*	X					X
Lipid Panel	X		X	X	X	X
EndoPAT measurement			X	X	X	X
IP dispensed			X	X	X	
IP returned				X	X	X
TLC Counseling	X	X				
3-day Food records dispensed	X		X	X	X	
3-day Food records returned			X	X	X	X
Study diary dispensed			X	X	X	
Study diary returned				X	X	X
Compliance calculated				X	X	X
Adverse events assessed				X	X	X