Statistical Analysis Plan

A Prospective, Double Blind, Randomized, Placebo-controlled Trial of Antroquinonol in Patients with Hypercholesterolemia and Hyperlipidemia

PROTOCOL NO.	**GHLIP-2-001**
SAP VERSION	**V1.0**
SAP DATE	**09-Feb-2018**
SPONSOR	**Golden Biotechnology Corporation**
PREPARED BY	**Isa Chen/Bestat Pharmaservices Corp.**

TITLE PAGE

A Prospective, Double Blind, Randomized, Placebo-controlled Trial of Antroquinonol in Patients with Hypercholesterolemia and Hyperlipidemia

PROTOCOL NO.	GHLIP-2-001
INVESTIGATIONAL DRUG	Antroquinonol (Hocena®)
INDICATION	Hypercholesterolemia and Hyperlipidemia
SPONSOR	Golden Biotechnology Corporation
PRINCIPAL INVESTIGATOR(S)	Fu-Tien Chiang, M.D. 江福田 教授 National Taiwan University Hospital
DATE OF FIRST ENROLLMENT	02-Nov-2016
DATE OF STUDY COMPLETION (LAST PATIENT LAST VISIT):	Expected on 30-Sep-2018
DATE OF DATABASE LOCK	Expected on 15-Oct-2018
SAP VERSION/DATE:	V1.0/ 09-Feb-2018

This study was performed in compliance with Good Clinical Practices (GCP) including the archiving of essential documents.

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ABBREVIATIONS

ABBREVIATIONS	DEFINITION
ABI	Ankle-brachial Index
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
baPWV	Brachial-ankle Pulse Wave Velocity
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CDMS	Clinical Data Management Systems
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CV	Cardiovascular
CV(%)	Coefficient of Variation
CVD	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
eGFR	Estimated glomerular filtration rate
GCP	Good Clinical Practice
ECG	Electrocardiogram

HDL-C	High-density Lipoprotein Cholesterol
HF	Heart Failure
hsCRP	High Sensitivity assay of C-reactive Protein
HU	Hounsfield Unit
ICH	International Conference on Harmonization
IL-1	Interleukin 1
IL-6	Interleukin 6
ITT	Intent-to-Treat
kg	Kilogram
LDL-C	Low-density Lipoprotein Cholesterol
LDL-R	Low-density Lipoprotein Receptor
m	Meter
m^2	Meters Squared
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PT	Preferred Term
PP	Per-Protocol
RBC	Red blood cell
SAE	Serious Adverse Event
SAS	Statistical Analysis System®
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class

SOP	Standard Operating Procedure
TC	Total Cholesterol
TG	Triglyceride
WBC	White blood cell

1 PREFACE

Dyslipidemia is a health risk, and epidemiologic studies have shown a link between total cholesterol levels and the risk of cardiovascular diseases (CVD). Previous studies have shown that lowering the levels of total and low-density lipoprotein cholesterol (LDL-C) are associated with decreasing in cardiac morbidity and mortality, whilst epidemiological evidence consistently indicate moderate and highly significant associations between triglyceride (TG) values and coronary heart disease risk [1]. Studies have shown that Antroquinonol® enhances the expression of low-density lipoprotein receptor (LDLR) genes in liver cells responsible for the removal of cholesterol in low-density lipoprotein cholesterol (LDL-C) from the blood stream and significantly increased high-density lipoprotein cholesterol (HDL-C) level ($p<0.001$) in plasma compared to vehicle control. These results demonstrate the potential applications of Antroquinonol® in treating hyperlipidemia and prevent associated CVDs. In this study, Antroquinonol® will be served as the study treatment to assess the reduction of TG in comparison with placebo in patients with hypercholesterolemia and hyperlipidemia after 12 weeks.

2 PURPOSE

The purpose of this SAP is to outline the planned statistical analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol GHLIP-2-001. The planned analyses identified in this SAP will be included in regulatory submission and/or future manuscripts. Also exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not

identified in this SAP performed will be clearly identified in the respective CSR.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is to demonstrate the reduction of TG by Antroquinonol, in comparison with placebo, after 12 weeks of treatment in patients with hypercholesterolemia and hyperlipidemia.

3.1.2 Secondary Objectives

Secondary objectives include the evaluation of the effects of Antroquinonol in comparison with placebo on other lipid parameters, left ventricular diastolic function, arterial stiffness, and fatty liver after 12 weeks of treatment. The safety and tolerability of Antroquinonol will be monitored as well.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary efficacy endpoint is the percentage change of TG by Antroquinonol, in comparison with placebo, after 12 weeks of treatment in patients with hypercholesterolemia and hyperlipidemia.

3.2.2 Secondary Endpoints

1. The effect of Antroquinonol in comparison with placebo on the percentage change in total cholesterol, HDL-C, LDL-C and HDL/LDL ratio from baseline after 12 weeks of treatment.
2. The effect of Antroquinonol on the ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/E' ratio) with tissue Doppler imaging and baPWV and ABI via a non-invasive arterial stiffness measurement.
3. The effect of Antroquinonol on the fatty liver prognostic with CT scan.

3.2.3 Safety Endpoints

1. Changes in laboratory examination including hematological, biochemical parameters, and urinary analysis.
2. Changes in electrocardiogram test, vital signs, and physical examinations.
3. Analysis of adverse events.
4. Compliance and tolerability of the study drug

4 STUDY METHOD

4.1 Overall Study Design and Plan

The study design is constructed as a multi-center, prospective, double-blind, randomized, placebo-controlled study to assess the reduction of TG by Antroquinonol, in comparison with placebo, after 12 weeks of treatment in patients aged between 20 and 75 years with hypercholesterolemia and hyperlipidemia. Enrolled patients are randomized in 1: 1: 1: 1 ratio to Antroquinonol 150 mg, Antroquinonol 100 mg, Antroquinonol 50 mg, or placebo.

4.1.1 Study Flow Chart

Flow Chart of the Study Schedule

Procedure	Screening *	Randomize	Treatment Period			Follow-up
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Interval	Day -14	Day 1 (Week 1)	Day 29 (Week 5)	Day 57 (Week 9)	Day 85 (Week 13)	Day 99 (Week 15)
Allow Window	-	-	±3	±3	±3	±3
Informed Consent	X					
Assessment of Eligibility Criteria	X					
Medical History	X					
Demographic	X					
Vital Signs [1]	X	X	X	X	X	X
Anthropometric measures [2]	X	X	X	X	X	X
Electrocardiogram		X			X	
Physical Examination	X	X	X	X	X	X
Urine Pregnancy Test	X					
Randomization [3]		X				
Drug Dispense		X	X	X		
Drug Return			X	X	X	
Efficacy Assessment						
Serum Lipid [4]	X	X	X	X	X	X
baPWV and ABI		X			X	
Image Monitoring [5]		X			X	
Biomarker Assessment						
CRP and Cytokine [6]		X			X	X
Safety Assessment						
CBC and WBC differential [7]		X			X	X
Biochemistry [8]	X	X	X	X	X	X
Urinary Exam [9]		X			X	X

Concomitant Therapy	X	X	X	X	X	X
Adverse Event		X	X	X	X	X

* A wash-out period of 2 weeks will not be applied to patients prior treated with medication which does not affect serum lipid level.

1. Vital signs: pulse rate, body temperature, respiratory rate, and blood pressure (including systolic blood pressure (SBP) and diastolic blood pressure (DBP)).
2. Including height, weight, waist circumference, and BMI (calculated by kg/m^2)
3. Subjects who meet the eligibility criteria will be randomized into treatment arms. If the eligibility is confirmed and a wash-out period is not needed for the subject, based on investigator's judgements the blood test required at V2 can be replaced by the data obtained 14 days before V2.
4. Serum lipids: total cholesterol, triglycerides, HDL-C, LDL-C, LDL/HDL ratio. Serum lipid results obtained 3 days prior to V1 is acceptable.
5. Doppler color flow mapping, and CT scan of the liver. CT scan will not be scheduled at visit 5 on subjects without fatty liver. Results of Doppler color flow mapping and CT scan of the liver obtained between V1 and V2 are acceptable.
6. hsCRP, IL-1, IL-6, and TNF-alpha.
7. WBC, RBC, Hb, Hct, RDW, platelet, MCV, MCH, MCHC, neutrophil-band and segment, lymphocyte, monocyte, eosinophil, and basophil.
8. Biochemical exam: AST, ALT, CPK, BUN and serum creatinine: visit 2 to visit 6; albumin, total bilirubin, direct bilirubin, ALP, total protein: V2, V5 and V6. At screening visit, serum creatinine shall be run for estimating glomerular filtration rate (GFR) and data obtained 3 days prior to V1 is acceptable.
9. Urinary exam: routine urine test (pH, protein, glucose, ketone, blood, urobilinogen, bilirubin, nitrite, leukocyte) and clinical microscopy.

4.1.2 Schedule of Assessments

Screening activities:

Before being enrolled to the study, patients should complete informed consent, review of medical history, physical examination, blood samples for lipid profile and biochemistry, demographic, anthropometric measures, urine pregnancy test, vital signs, and concomitant therapy record.

Every study visit day including Day1, 29, 57, 85, 99:

The patient who meets all the entry criteria are eligible for the study. During the study period, the patient have to undergo biochemistry assessment, vital signs measurements, anthropometric measures, physical examination, serum lipid test, concomitant therapy record, and adverse event assessment.

Every study visit day including Day 1, 85, 99:

During the study period, biomarker assessment, CBC and WBC differential, and urinary exam are conducted.

Every study visit day including Day 1, 85:

During the study period, electrocardiogram, baPWV, ABI, and image monitoring are performed.

Every study visit day including Day 1, 29, 57, 85:

Dispense new study drug pack to the patient (Day 1, 29, 57), collect unused portion of previous pack from the patient (Day 29, 57, 85), and ensure accountability information on patients' drug accountability log.

4.2 Selection of Population

4.2.1 Inclusion Criteria

1. Adults of either sex 20 to 75 years of age, inclusive, with a diagnosis of nonfamilial hypercholesterolemia or mixed hyperlipidemia as one of the following:
   - TG between 150 mg/dL and 500 mg/dL, and cholesterol between 160 mg/dL and 250 mg/dL
   - TG between 150 mg/dL and 500 mg/dL and LDL-C > 130 mg/dL).
2. Subject must be free of any clinically significant disease, other than nonfamilial hypercholesterolemia or mixed hyperlipidemia that would knowingly interfere with study evaluations.

3. A wash-out period of 2 weeks will be applied to patients prior treated with lipid-lowering medication.
4. Subject must be willing to adhere to protocol requirements, and provide written informed consent.
5. Female of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

4.2.2 Exclusion Criteria

1. Patients with secondary dyslipidemia caused by diabetes mellitus, hypothyroidism, obstructive liver disease, chronic renal failure or drugs which can increase LDL-C level (e.g. retinoids, cyclosporine A and phenothiazines) or decrease HDL-C level (e.g. progestins, androgens, β-blockers, probucol and anabolic steroid).
2. Patients with lifestyle that may interfere treatment efficacy, such as alcoholism or drinking habits more than 3 times per week, late dinner, late night supper, frequent oversea business traveler, frequent social gathering, and patients who cannot anticipate a diet control and lifestyle changes.
3. Patients with diabetes or history of coronary artery disease (has had myocardial infarction, cardiac intervention, cerebrovascular accident/stroke or transient ischemic attack less than 6 months prior to Visit 1).
4. Patients with hypertension that is uncontrolled defined as 2 consecutive measurements of sitting blood pressure of systolic >140 mmHg or diastolic > 90 mmHg at Visit 1.
5. Patient has a known hypersensitivity to Antroquinonol or related compounds.
6. Patient with uncontrolled intercurrent illness including, but not limited to, acute decompensated HF (exacerbation of chronic HF manifested by signs and symptoms that may require IV therapy), right heart failure due to severe pulmonary disease, diagnosed peripartum or chemotherapy induced cardiomyopathy within the 12 months prior to visit 1, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Patients with a history of heart transplant or who are on a transplant list or with left ventricular assistance device (LVAD device).

8. Patients with documented ventricular arrhythmia with syncopal episodes within the past 3 months prior to visit 1 that remained untreated.
9. Patients with confirmed severe primary pulmonary, renal (eGFR<30 ml/min/1.73 m^2) or hepatic (Child-Pugh B/C classification) disease.
10. Patients who can't stop current lipid lowering drug treatments based on investigator's judgement.
11. Patients with any malignancy, treated or untreated, within the past 5 years of Visit 1 whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin or carcinoma in situ of the cervix.
12. Female patient during pregnancy, lactation or breastfeeding.
13. Patient has any other life-threatening complications.
14. Patient who is considered unreliable as to medication compliance or adherence to scheduled appointments, or inappropriate for inclusion determined by the investigators.
15. Any other reasons addressed by the investigators.

4.3 Randomization and Blinding

According to the double-blind study design, enrolled patients are randomized in 1: 1: 1 :1 ratio to receive either Antroquinonol 150 mg, Antroquinonol 100 mg, Antroquinonol 50 mg, or placebo. The randomization sequence was generated using SAS version 9.3 with blocks of variable size and random seeds to ensure that allocation concealment is not violated through guessing of the allocation sequence at the end of each block. The aforementioned randomization code list was generated by the CRO and provided to Golden Biotechnology Corporation in order to pack and label the study drugs. Randomization data would not be accessible by anyone else involved in the study. The corresponding study group of individual subjects were recorded in a sealed envelope and were kept strictly confidential until the time of data lock. For this multi-center study, centralized randomization was applied. The investigator confirmed the subject

fulfilled the inclusion and exclusion criteria and informed the randomization center. The sponsor's independent staff provided the randomization number in order. The study drugs labeled with randomization number was provided according to the request from each site.

After enrollment, subjects were randomly assigned to receive one of the study treatments in a double-blind fashion. The identity of the treatments were concealed by the use of study drugs. The placebo was masked by the same appearance, odor and taste as the study drug (Antroquinonol), and used as well. Subjects, investigator, site staff, persons performing study assessments and data analysts remain blinded to the treatment assignment from the time of randomization until data lock.

5 SAMPLE SIZE DETERMINATION

The sample size estimation of this study is using two-sample T-test under one-sided significance level 0.025, power 90%. Based on the Davidson's study, the TG reduction percentage change of 130 mg Fenoribrate from baseline to last visit was 36.6% for subjects who were treated with the study treatment, and the standard deviation was 2.4% and 5.3% for the study treatment and the control treatment. Assuming a drop-out rate of 20%, a sample size of 120 patients (30 patients per arm) were required to provide 96 evaluable patients (24 patients for each group) which indicates an achievement of 80% completion rate.

6 SEQUENCE OF PLANNED ANALYSES

6.1 Interim Analyses and Data Monitoring

No interim analysis will be performed for this study.

6.2 Final Analyses and Reporting

All final planned analyses identified in the protocol and in this SAP will be performed only after the last patient has completed assessments scheduled for the 12-week study period and the database has been cleaned and locked. A blinded data review will be conducted prior to database lock and completion of the final analyses. In addition, no database may be locked, random code un-blinded, or analyses completed until this SAP has been approved.

Key Statistics and study results will be made available to Bestat Pharmaservices Corp. following database lock and prior to completion of the final CSR.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, all be documented and reported in appendices to the CSR. Any results from unplanned analyses will also be clearly identified in the text of the CSR.

7 GENERAL CONSIDERATIONS

7.1 Relevant SOPs and Policies

The data manager (DM) will carry out verification procedures upon double data entry completion. Data entered in the first database has to be verified against the data entered in the second database for comparison and verification purposes. All discrepancies shall be recorded and data verification output shall be generated after this process. The DM verify the discrepancies between first entry and second entry against the hard copy CRF. All verified data must be uploaded to the updated database(s). Data verification output and relevant records will be stored properly and securely.

To ensure the data reliability, DM validate data based on data validation plan and reconfirm

those unreliable values for all collected data includes safety and efficacy data. The locked data will be treated as analyzable data.

7.2 Timing of Analyses

The final analyses will be performed when the last subjects have completed the study or permanently discontinued the study, all queries are solved, protocol deviation/violation has been identified, database has been locked and the statistical analysis plan with detail methods has been finalized and approved.

7.3 Missing Data

Last observation carried forward (LOCF) will be used to approach the missing data of primary endpoint in Intent-To-Treat (ITT) population. For each individual, missing values occurs in efficacy variable (i.e., TG) will be replaced by the later point. If more than two data are missing the following assessment, the last non-missing value will be used to fill in each missing observation. The variable TG related with the primary endpoint assessment will be presented by LOCF method.

No missing data will be imputed for the secondary efficacy or safety analyses.

7.4 Analysis Populations

ITT population, Per-Protocol (PP) population and Safety populations are three populations for statistical analysis. The ITT population and PP population are used in analysis of efficacy variables, and the safety population perform in analysis of safety variables.

7.4.1 Intent-to-Treat Population (ITT)

The ITT population includes all randomized patients who meet all inclusion criteria and

exclusion criteria, take at least one study medication and have at least one post-baseline measurement.

7.4.2 Per Protocol Population

The PP population is a subset of the ITT population and includes all randomized patients who complete 12 weeks of treatment without major protocol violation.

The definition of major protocol violations include

- violate the enrollment criteria,
- use of prohibited medications indicated to treat dyslipidemia,
- drug compliance less than 70%.

7.4.3 Safety Population

All subjects who received at least one study medication will be included in the safety analysis population.

7.5 Covariates and Subgroups

The primary efficacy endpoint for assessing the superiority of Antroquinonol (50mg, 100mg, and 150mg) to placebo is the mean percentage reduction change of TG in patients with hyperlipidemia by using analysis of covariance (ANCOVA) model using baseline measurement as covariates, if the differences in baseline characteristics, such as gender, age, weight etc., are observed, for comparing the effectiveness between the treatment groups and placebo.

7.6 Derived and Computed Variables

The following derived and computed variables have been initially identified. It is expected that

additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary endpoint or key secondary endpoints. An additional derived or computed variables will be identified and document in the SAS programs that create analysis files.

- Age (years) = (date of giving inform consent – date of birth)/365.25
- BMI (kg/m^2) = Weight (kg) / Height^2 (m^2)
- Treatment Compliance (%) = $\frac{\text{Quantity of total dispensed} - \text{Quantity of total returned}}{\text{Treatment period (84 days)}} \times 100\%$
- Percentage change from baseline of TG (%) = $\frac{Day85\ (TG) - Day1\ (TG)}{Day1\ (TG)} \times 100\%$

7.7 Adjustments for Multiplicity

For comparison of percentage change in TG of three groups with placebo, 100mg vs. 50 mg, and 150mg vs. 100mg, the post hoc tests will be used to detect which group differ from the rest while statistical significance of ANCOVA or Kruskal-Wallis test. For ANCOVA, the required significance criterion alpha is 0.05 divided by the total number of tests. To correct the multiple testing for primary endpoint, the p-value will be adjusted according to Bonferroni's method to reject the null hypothesis (p-value <0.05/m, m= number of tests). In addition, two independent t-test will also be used for pairwise comparison (p-value=0.05 for all multiple tests). For Kruskal-Wallis test, two independent t-test or Wilcoxon rank-sum test will be used for pairwise comparison (p-value=0.05 for all multiple tests).

7.8 Multi-center Studies

Total efficacy-evaluable patients will be enrolled from multiple study sites, i.e., National Taiwan University Hospital, China Medical University Hospital, National Cheng Kung University

Hospital, Far Eastern Memorial Hospital, Taipei Veterans General Hospital, and Chang Gung Memorial Hospital, Linkou branch. With the intention of pooling the data for analysis, all the investigators from participating institutions will follow the study protocol and conduct the clinical trial to improve the consistency across centers. All collected clinical data will be managed, centralized and summarized with respect to demographic characteristics, and efficacy and safety observations.

7.9 Data Management System and Analysis Software

The data collected will be entered into the study database against the paper CRF and stored in the Clinical Data Management Systems (CDMS). The data backup is exhibited by data management personnel. The data will be exported to Statistical Analysis System® (SAS) for Windows (Version 9.4, SAS Institute, Cary, North Carolina, USA) to generate the subject listings, tabulations, and statistical analyses.

7.10 Coding Dictionary

In order to create a standard language that is comparable across all therapeutic teams and provide standardization for statistical analysis, adverse events recorded on the paper CRF will be coded by medical dictionaries/thesaurus. In this study, the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 will be used to map adverse events verbatim to Preferred Terms (PT) and System Organ Class (SOC).

7.11 Data Handling and Transfer

All collected clinical data or external data will be managed centralized and stored in the clinical data management systems. The system of variable coding will follow rules of Bestat Pharmaservices Corp.

7.12 Programming Specifications

The summary statistics for continuous variables will be entitled as Number, Mean±SD, Median, Range and 95% C.I. in the table, which represent the number of observations, mean value plus/minus standard deviation, median value of observations, minimum and maximum, lower bound and upper bound of the 95% confidence interval. Range and 95% C.I. are given in parentheses.

Unless otherwise noted, the summary statistics for continuous variables will be printed out to one decimal place except for the standard deviation and confidence interval. The standard deviation and confidence interval will be expressed to 2 decimal places.

In analysis of categorical variable, descriptive statistics will be entitled as frequencies and percentages. All table percentages will be reported with two decimal points unless otherwise specified.

All statistical tests will be conducted under a two-tailed, significance level of 0.05 with related p-value. The p-value will be reported to three decimal places. An asterisk indicates the statistical significance. P-value less than 0.001 will be reported as "< 0.001*" and p-value greater than 0.999 will be expressed as "> 0.999".

8 SUMMARY OF STUDY DATA

Continuous variables will be summarized by descriptive statistics: number of observations, mean, median, standard deviation, range and 95% C.I. Frequency counts and percentages (based on non-missing sample size) of observed levels will be reported for categorical variables.

8.1 Disposition of Subject and Withdraws

Participants who signed the informed consent form will follow study-related procedures described in the protocol till the end of study. However, subjects are free to withdraw from the study at any time. The number of screened, randomized, reached study completion will be counted and summarized. The reason causing the discontinuation will be provided as listing report as well. The allocation in each treatment group will be specified and the size of analysis populations will be determined by treatment.

8.2 Protocol Violation and Deviations

Protocol deviations includes but do not restrict to the following:

- Out of visit and procedure window.
- Deviations from the expected dispensing regimen.
- Intentional deviation from the protocol, GCP or regulations by study personnel in a non-emergency setting.

Protocol violations includes the following:

- Violate the eligibility founded after the randomization.
- Failure to obtain valid informed consent.

8.3 Demographics

The following demographic and baseline characteristics will be ascertained at the time of study recruitment: gender, age, height, weight, BMI, pregnancy status (females only), medical history, physical examination, and concomitant medications. Continuous data will be summarized by descriptive statistics using number of specific item, mean, median, standard deviation,

maximum and minimum. Frequencies and percentages are tabulated for categorical data. The analysis of baseline characteristics will be performed using safety population.

If the differences in baseline characteristics are observed, the multiple linear model will adjust for the significant variables in the primary analysis. The baseline demographic characteristics will be compared using Chi-square test or Fisher's exact test for categorical variables and t-test or Wilcoxon Rank-Sum test for continuous variables.

8.4 Baseline and Screening Conditions

8.4.1 Baseline Medical History

No coding or analysis items for medical history of subjects will be planned. The listing report will present the raw medical history record of subjects.

8.4.2 Baseline Physical Exam

Results of baseline physical examination for abnormality will be listed.

8.5 Prior and Concurrent Medications

Data coding for Adverse Events will be based on pre-existing/concurrent conditions or treatments. All prior and concurrent data will be presented by patients and by treatment in the listing report.

8.6 Treatment Compliance

Patients will be instructed to take a total of three capsules of Antroquinonol and/or placebo in different combination once per day and return to the study site on the next visit. A record of the

number of capsules dispensed, taken and returned for each patient must be documented on the CRF. Compliance will be assessed from the information recorded in the CRF, including study medication count, start and end date of therapy. The treatment compliance rate will be determined by the number of taken drugs divided by number of taken drugs divided by number of days of treatment taken × 3 capsules per day that should be taken and presented in the percentage format, given by:

- Treatment Compliance (%) = $\frac{\text{Quantity of total dispensed} - \text{Quantity of total returned}}{\text{Treatment period (84 days)}} \times 100\%$

9 STATISTICAL METHODS

9.1 Primary Hypothesis

The primary endpoint in a study is the percentage change from baseline of TG by Antroquinonol compared to placebo after 12 weeks. The primary hypothesis of the study is that:

H_0: the percentage change of TG score in four groups are equal versus

H_A: at least one of the percentage change of TG score in four groups is different

9.2 Test of Assumptions

The continuous variables will be compared using Student's t test (2 groups) or analysis of variance (> 2 groups). If the conditions for applying these tests are not met normality assumption, the Wilcoxon rank sum (2 groups) or Kruskal-Wallis (> 2 groups) non-parametric tests will be used. Comparison within group will be tested by using paired t test. If the normal assumption is violated, the Wilcoxon signed-rank test will be conducted. The category variables will be compared between groups using the Chi-square test if the theoretical total of each class studied is greater than 5. Otherwise Fisher's exact test will be used.

9.3 Primary Endpoint Analysis

The primary efficacy endpoint (percentage change of TG) for assessing the superiority of Antroquinonol (50mg, 100mg, 150mg) to placebo is the percentage change in patients with hyperlipidemia by using analysis of covariance (ANCOVA) model using baseline measurement as covariates (model 1). If the differences in baseline characteristics, such as gender, age, weight etc., are observed, for comparing the effectiveness between the treatment groups and placebo, the model will be performed by multiple linear model (model 2) to adjust characteristics.

Model 1: $Y_{\text{percentage change of TG (\%)}} = \beta_1 + \beta_2 X_{\text{treatment}} + \beta_3 X_{\text{baseline of TG}}$

Model 2: $Y_{\text{percentage change of TG (\%)}} = \beta_1 + \beta_2 X_{\text{treatment}} + \beta_3 X_{\text{baseline of TG}} + \beta_4 X_{\text{ significant characteristic in baseline}}$

If statistical significance of ANCOVA treatment effect is reached (p-value<0.05), Bonferroni's method, and two independent t-test (section 7.7) will be performed post hoc analysis for pairwise comparison of percentage change in TG (Antroquinonol 50 mg vs. Placebo, Antroquinonol 100 mg vs. Placebo, Antroquinonol 150 mg vs. Placebo, Antroquinonol 100 mg vs. Antroquinonol 50 mg and Antroquinonol 150 mg vs. Antroquinonol 100 mg).

If the normal assumption is violated for percentage change of TG in any treatments, Kruskal-Wallis test will replace ANCOVA. If statistical significance of Kruskal-Wallis test treatment effect is reached (p-value<0.05), two independent t-test or Wilcoxon rank-sum test will be performed post hoc analysis for pairwise comparison of percentage change in TG (Antroquinonol 50 mg vs. Placebo, Antroquinonol 100 mg vs. Placebo, Antroquinonol 150 mg vs. Placebo, Antroquinonol 100 mg vs. Antroquinonol 50 mg and Antroquinonol 150 mg vs. Antroquinonol 100 mg).

9.4 Secondary Endpoint Analyses

Analysis of other secondary efficacy endpoints (TC, HDL-C, LDL-C, and LDL/HDL ratio as well as the effect of Antroquinonol on E/E', baPWV and ABI and HU parameters) will be similar to the primary analysis of the primary endpoint by using ANCOVA model using baseline measurement as covariates, or using Kruskal-Wallis test when normal assumption is violated. Pairwise comparison will use two independent t-test or Wilcoxon rank-sum test, and performed significance level of 0.05 while statistical significance of ANCOVA or Kruskal-Wallis test treatment effect is achieved (Antroquinonol 50 mg vs. Placebo, Antroquinonol 100 mg vs. Placebo, Antroquinonol 150 mg vs. Placebo, Antroquinonol 100 mg vs. Antroquinonol 50 mg and Antroquinonol 150 mg vs. Antroquinonol 100 mg).

9.5 Safety Analyses

For the safety assessments, the information of adverse events will be described in detail. Count and percentage will be tabulated for the number of patients with AEs, number of total AEs, number of patients with AEs associated to study dosing and intensity. Adverse events will be coded by the Medical Dictionary for Regulatory Activities (MedDRA®) adverse event dictionary. All the AEs will be categorized by each represented Preferred Terms (PT) and System Organ Class (SOC), which will be tabulated by body system with related incidence rates. The clinical laboratory tests and electrocardiogram tests will be analyzed to separate subjects into normal and abnormal categories, with number of subjects and percentage of subjects in each category, and McNemar's test or Fisher's exact test will then be applied to test the changes between each visit.

9.6 Subgroup Analyses

The primary and secondary endpoints analyses will be performed by classified subgroup using ITT population and PP population. In addition, specified categorical or numeric characteristics if the demographic variables are statistically and clinically significant. The identified numeric variable will be classified by an appropriate cut-off point.

9.7 Interpretation and Conclusion

All tests are two-tailed unless otherwise specified and the overall significant level is set to be 0.05. When the number of hypothesis in a test is increased, the Bonferroni correction would be used to test each of the individual tests at a significance level of 0.05/m (m= number of tests=5, section 9.3). Statistical significance will be demonstrated if the p-value is less than the significance level of test. Regardless of the outcome declared statistically significant, all results could be stated on the Clinical Study Report (CSR).

10 SAFETY ANALYSES

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Adverse Events
  - AEs and SAEs
  - AEs leading to withdrawal
  - Any Deaths

- Clinical Laboratory Investigations
- Other Safety measures: vital signs, ECG, physical examinations

Safety assessments consist of monitoring and recording all adverse events, laboratory tests, vital signs and physical examinations. Adverse event incidence rates in each group will be summarized by system organ class and preferred terms. Each subject will be counted only once within a system organ class or a preferred term and any repetitions will be ignored.

10.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary Version 20.0.

10.1.1 All Adverse Events

Summaries of incidence rates (frequencies and percentages), intensity, and relationship to study drug of individual AEs by System Organ Class and Preferred Term (MedDRA) will be prepared. Each patient will be counted only once within each preferred term per study period. If a patient experiences more than one AE within a prepared item for the same recording period, only the AE with the strongest relationship or the greatest intensity, as appropriate, will be included in the summaries of relationship and intensity.

Summaries will be presented by treatment group for Antroquinonol. Fisher's exact test will he used to compare rates for System Organ Classes across treatment groups. A similar summary by treatment group will be presented for all patients in the Safety Population.

Counts of AEs by maximum intensity will be presented for patients in the Safety Population by treatment group, grouped by the treatment the patient had received most recently prior to the

AE. Only AEs beginning at or after the beginning of study drug administration will be included. Similarly, counts of AEs by strongest relationship to study drug will be presented.

A data listing will also be presented showing all AEs, which started prior to the administration of any study drug.

10.1.2 Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of AEs leading to withdrawal, by treatment group, System Organ Class, and Preferred Terms, will be prepared for the Safety Population. No statistical tests will be performed.

A data listing of AEs leading to withdrawal will also be provided, displaying details of the event(s) captured on the CRF.

10.1.3 Serious Adverse Events

Serious adverse events reconciliation will be performed by Data Management, Clinical Research, and Golden Drug Safety and Pharmacovigilance via data listings.

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group. System Organ Class, and Preferred Term will be prepared for the Safety Population. No statistical tests will be performed.

A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF. Serious adverse event narratives will be provided for the CSR by the Golden Drug Safety and Pharmacovigilance Department.

10.1.4 Deaths

If any patients die during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

10.1.5 Other AE Assessments

No other assessments or analysis are planned.

10.2 Clinical Laboratory Evaluations

Descriptive summaries (mean, SD, median. minimum. and maximum for each group with related 95% confidence interval.) of changes from baseline will be presented for clinical laboratory values by treatment for the Safety Population.

The number of patients with clinical laboratory values below, within, or above normal ranges, pre-procedure versus post-procedure will be tabulated for each test, for the Safety Population by treatment group. Pre- and post-procedure values will also be presented with an analysis of mean changes from baseline. Laboratory assessment results will be classified to normal or abnormal, and will be tabulated with related frequency and percentages. The shift tables of laboratory results will also be provided.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

10.3 Other Safety Measures

- Vital Signs

Descriptive statistics of actual, values and changes from baseline will be calculated for heart rate, Blood pressure, body temperature, weight, waist circumference, hip circumference and body fat.

- 12-Lead ECG

Individual ECG values will be listed and summarized by descriptive analysis. Comparisons between baseline ECG and post-screening ECGs result will also be evaluated.

- Physical Examinations

Results of physical examination for abnormality will be listed.

11 REPORTING CONVENTIONS

The following reporting conventions will be adopted for the SAP. These conventions will enhance the review process and help to standardize presentation with common notations.

11.1 General Reporting Conventions

All tables, figure, and data listings will have the name of the program and a date/time stamp on the bottom of each output and will be presented in Landscape Orientation. Unless presented as part of the text in a CSR.

All titles will be left justified and top of the page, and all footnotes will be left justified and the bottom of a page. Missing values for both numeric and character variables will be presented as blanks or "." in a table or data listing.

All data values will be presented as MM/DD/YYYY (e.g., 08/29/2001) format. A four-digit year is preferred for all dates.

11.2 Population/Statistic Summary Conventions

Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as "Population: [name of population]" and will be identical in name to that identified in the protocol or SAP.

Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) ITT, (b) PP or Per-Protocol, and (c) Safety.

Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.

All population summaries for categorical variables will include categories that the patients had a response in these categories.

All population summaries for continuous variables will include: N. mean, SD, minimum, and maximum. Other summaries (e.g. median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate. All percentages are rounded and reported to two decimal points.

Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

12 SUMMARY OF CHANGES TO THE PROTOCOL

No change in non-statistical and statistical analysis to the protocol.

13 REFERENCES

1. Protocol No.: GHLIP-2-001 version 2.1
2. ICH harmonized tripartite Guideline: E9 - Statistical Principles for Clinical Trials
3. ICH harmonized tripartite Guideline: E3 – Structure and Content of Clinical Study Reports

14 APPENDIX

14.1 Mock-up Tables

- **Statistical Table**
- **Data Listing**

Protocol: CYBBV1302 **Study Sponsor: Chuang-Yi Biotech Corp., Ltd.**

Statistical Table

Page 1 (LAST PAGE)
Table 14.1.2.1 Summary of Demographic and Baseline Characteristics (Safety Population)

Characteristics	Antroquinonol 50 mg (N=)	Antroquinonol 100 mg (N=)	Antroquinonol 150 mg (N=)	Placebo (N=)	P-Value
Age &					
NUMBER					
MEAN					
S.D.					
RANGE					
95% C.I.					
Gender #					
MALE					
FEMALE					
Race #					
ASIAN					
TAIWAN INDIGENOUS					
CAUCASIAN					
BLACK					
OTHER					

Program name: Antro_T_DEMO.sas Programmer:
RANGE: (Minimun, Maximum); S.D.: Standard Deviation; CI: 95% Confidence Interval
&: P-value was conducted by T-test/Kruskal-Wallis test for Continuous Variables
#: P-value was conducted by Chi-square/Fisher's exact test for Categorical Variables

Data Listing

Listing 16.2.1.1 --- Subject Early Termination

Page 1 of 2

Site No.	Screening No.	Subject No.	Did Subject Complete the Study?	What Was the Primary Reason for Early Termination/Withdrawal?

Site No.: 1=National Taiwan University Hospital, 2=China Medical University Hospital, 3=National Cheng Kung University Hospital, 3=National Cheng Kung University Hospital, 4=Taipei Veterans General Hospital, 5=Far Eastern Memorial Hospital, 6=Chang Gung Memorial Hospital, Linkou branch

14.1 Planned Tables

The contents of Statistical analysis tables and data listing follow ICH E3 Guidelines for tables, figures and graphs.

Statistical Tables

14.1 Demographic Data

Table 14.1.1.1 Summary of Subject Disposition by Treatment Group

Table 14.1.1.2 Primary Reason for Discontinuation

Table 14.1.2.1 Summary of Demographic and Baseline Characteristics (Safety Population)

14.2 Efficacy Data

Table 14.2.1.1 Primary Endpoint: Percentage change of TG after 12 Weeks (ITT)

Table 14.2.1.2 Primary Endpoint: Percentage change of TG after 12 Weeks (PP)

Table 14.2.2.1 Secondary Endpoint: Percentage change of TC, HDL-C, LDL-C, and LDL/HDL after 12 Weeks (ITT)

Table 14.2.2.2 Secondary Endpoint: Percentage Change of TC, HDL-C, LDL-C, and LDL/HDL after 12 Weeks (PP)

Table 14.2.3.1 Secondary Endpoint: Percentage Change of E/E', baPWV, ABI, and HU after 12 Weeks (ITT)

Table 14.2.3.2 Secondary Endpoint: Percentage Change of E/E', baPWV, ABI, and HU after 12 Weeks (PP)

14.3 Anthropometric measures

Table 14.3.1.1 Summary of Anthropometric measures (Safety Population)

Table 14.3.1.2 Summary of Mean Change from Baseline in Anthropometric measures (Safety Population)

14.4 Safety Data

Table 14.4.1.1 Summary of Vital Sign by Visit (Safety Population)

Table 14.4.1.2 Summary of Mean Change from Baseline in Vital Sign (Safety Population)

Table 14.4.2.1 Summary of of Physical Examinations (Normal/Abnormal) (Safety Population)

Table 14.4.2.2 Transition Table of Physical Examinations (Safety Population)

Table 14.4.3.1 Summary of baPWV, ABI, E/E', and HU (Safety Population)

Table 14.4.3.2 Summary of of 12-Lead ECG, baPWV, ABI, E/E', and HU (Normal/Abnormal) (Safety Population)

Table 14.4.3.3 Transition Table of 12-Lead ECG, baPWV, ABI, E/E', and HU after 12 Weeks (Safety Population)

Table 14.4.4.1 Summary of Laboratory Assessment-Lipid Profile (Safety Population)

Table 14.4.4.2 Summary of Laboratory Assessment-Serum Chemistry (Safety Population)

Table 14.4.4.3 Summary of Laboratory Assessment-Hematology (Safety Population)

Table 14.4.4.4 Summary of Laboratory Assessment-Biomarkers (Safety Population)

Table 14.4.4.5 Summary of Laboratory Assessment-Urinary Exam (Safety Population)

Table 14.4.5.1 Summary of Laboratory Assessment-Lipid Profile (Normal/Abnormal) (Safety Population)

Table 14.4.5.2 Summary of Laboratory Assessment-Serum Chemistry (Normal/Abnormal) (Safety Population)

Table 14.4.5.3 Summary of Laboratory Assessment-Hematology (Normal/Abnormal) (Safety Population)

Table 14.4.5.4 Summary of Laboratory Assessment-Biomarkers (Normal/Abnormal) (Safety Population)

Table 14.4.5.5 Summary of Laboratory Assessment-Urinary Exam (Normal/Abnormal) (Safety Population)

Table 14.4.5.6 Summary of Laboratory Assessment-Microscopy (Normal/Abnormal) (Safety Population)

Table 14.4.6.1 Transition Table of Laboratory Assessment-Lipid Profile (Safety Population)

Table 14.4.6.2 Transition Table of Laboratory Assessment-Serum Chemistry (Safety Population)

Table 14.4.6.3 Transition Table of Laboratory Assessment-Hematology after 12 Weeks (Safety Population)

Table 14.4.6.4 Transition Table of Laboratory Assessment-Biomarkers after 12 Weeks (Safety Population)

Table 14.4.6.5 Transition Table of Laboratory Assessment-Urinary Exam after 12 Weeks (Safety Population)

Table 14.4.6.6 Transition Table of Laboratory Assessment-Microscopy after 12 Weeks (Safety Population)

Table 14.4.7.1 Summary of Subject Compliance for the Study Drugs (Safety Population)

Table 14.4.8.1 Summary of Adverse Events by Treatment Groups (Safety Population)

Table 14.4.8.2 Summary of Adverse Events by MedDRA Coding (Safety Population)

Table 14.4.9.1 Summary of Concomitant Medication by Treatment Groups (Safety Population)

Table 14.4.10.1 Summary of Concomitant Therapies by Treatment Groups (Safety Population)

Data Listing

16.2.1 Discontinued Subjects

Listing 16.2.1.1 --- Subject Early Termination

16.2.2 Subjects Eligibility

Listing 16.2.2.1 ---Treatment groups and Population

Listing 16.2.2.2 --- Inclusion Criteria

Listing 16.2.2.3 --- Exclusion Criteria

16.2.3 Demographics Data

Listing 16.2.3.1 --- Demographics

Listing 16.2.3.2 --- Medical History

16.2.4 Safety Response

Listing 16.2.4.1 --- Vital Sign Measurements

Listing 16.2.4.2 --- Urine Pregnancy Test

Listing 16.2.4.3 --- Physical Examinations

Listing 16.2.4.4 --- 12-Lead Echocardiogram

Listing 16.2.4.5 --- Concomitant Medications

Listing 16.2.4.6 --- Concomitant Therapies

16.2.5 Efficacy Response

Listing 16.2.5.1 ---TG, TC, HDL-C, LDL-C, and LDL/HDL ratio

Listing 16.2.5.2 --- baPWV, ABI attenuation, E/E' ratio, and HU attenuation

16.2.8 Reporting Adverse Events

Listing 16.2.8.1 --- Adverse Events

16.2.9 Laboratory Measurements

Listing 16.2.9.1 --- Hematology

Listing 16.2.9.4 --- Serum Chemistry

Listing 16.2.9.5 --- Urinalysis

Listing 16.2.9.2 --- Biomarkers

Listing 16.2.9.3 --- Microscopy

16.2.10 Other Correspondence

Listing 16.2.10.1 --- Visit Date and Subject Initials

Listing 16.2.10.2 --- Study Drug Dispensed

Listing 16.2.10.3 --- Comments