



## STATISTICAL ANALYSIS PLAN

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<b>Study Title:</b>	<i>A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Cyclo-Z in Patients with Obese Type 2 Diabetes</i>
<b>Phase:</b>	2
<b>Protocol Number:</b>	NMP-CYZ-P2-001
<b>Protocol Version/Date:</b>	Version 2.4 / 9 December 2016
<b>SAP Version/Date:</b>	Version 1.2 / 16 October 2017
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### STATISTICAL ANALYSIS PLAN APPROVAL

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### Document Version History

Version	Date	Author	Description of Changes
1.0	21 June 2017	Hyun Ji Kim	Initial version
1.1	29 August 2017	Hyun Ji Kim	<b>Modified the following by sponsor request.</b> 1. Added exploratory efficacy analysis for TAFGC. 2. Added paired t-test (or Wilcoxon signed-rank test) to analysis the change of efficacy endpoints within each group. 3. Deleted Analysis for unexpected adverse events.
1.2	16 October 2017	Hyun Ji Kim	<b>Modified the following by sponsor request.</b> 1. Added 1 exploratory efficacy endpoint – BMI. 2. Added exploratory efficacy analyses for BMI. 3. Updated calculation for TAFGC. 4. Added sponsor defined definitions for Hypoglycemia and Hyperglycemia 5. Added section for Subgroup Analysis. 6. Added section for Post-hoc Analysis.

**Table of Abbreviations**

<b>Abbreviation</b>	<b>Description</b>
AE	Adverse Event
ADDQoL	Audit of Diabetes-Dependent Quality of Life
BMI	Body Mass Index
BP	Blood Pressure
BSA	Bio-Statistics Associate
BSM	Bio-statistics Manager
BW	Body Weight
cGMP	Current Good Manufacturing Practice
CHP	Cyclo (His-pro)
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
Cyclo	Cyclic dipeptide
DBMS	Database Management System
DM	Diabetes Mellitus
DPP	Dipeptidyl Peptidase
DW	Distilled Water
eCRF	Electronic Case Report Form
EAS	Efficacy Analysis Set
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
G-K	Goto-Kakizaki
GLP	Good Laboratory Practice
GLP-1	Glucagon-like protein-1
GLUT-4	Glucose transporter-4
GMP	Good Manufacturing Practice
HbA1c	Hemoglobin A1c
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Insulin Degrading Enzyme
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MsSQL	Microsoft Structured Query Language
NIDDM	Non-insulin-dependent Diabetes Mellitus
ODBC	Open Database Connectivity
OGTT	Oral Glucose Tolerance Test
PT	Preferred Term

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SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
S-D	Sprague-Dawley
SEM	Standard Error of the Mean
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedure
TAFGC	Three-hour-area-average Above Fasting Glucose Concentration
TSH	Thyroid Stimulating Hormone
T3	Triiodothyronine
T4	Thyroxine
WHODRUG	World Health Organization Drug

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## 1. INTRODUCTION

This Statistical Analysis Plan (SAP) is developed to guide the details of the statistical analysis method of the phase 2 study to evaluate the efficacy and safety of Cyclo-Z in patients with obese type 2 diabetes. The SAP includes detailed definitions of the populations to be analyzed, the subject characteristics and the efficacy and safety endpoints, as well as the specific statistical analysis methods to be performed.

## 2. STUDY OBJECTIVE(S)

### 2.1 Primary Objective

The primary objective is to assess the dose-dependent efficacy of Cyclo-Z for the treatment of subjects with obese type 2 diabetes.

### 2.2 Secondary Objective

The secondary objective is to assess the safety of Cyclo-Z in the treatment of subjects with obese type 2 diabetes.

## 3. STUDY OVERVIEW

### 3.1 Study Design

#### 3.1.1 Overall Study Design

This is a double-blind, randomized, placebo-controlled, parallel-group comparison study to evaluate the efficacy and safety of Cyclo-Z vs. placebo in adult subjects with obese type 2 diabetes. Up to four sites may be utilized in the United States so that a total of 80 subjects (a potential 20% screening failure rate) may be screened for total 16-week study period (2 weeks for screening, 12 weeks for treatment, and 2 weeks for safety follow-up).

Subjects who meet preliminary inclusion and exclusion criteria at Screening will undergo a 2-week assessment period of record-keeping compliance. Subjects will be asked to record daily blood glucose values (fasting before breakfast and two hours after dinner) and study medication adherence throughout study participation.

Sixty-four (64) qualified subjects will be assigned randomly to either the placebo arm or to one of the three treatment groups requiring the oral intake of a single gel capsule of Cyclo-Z or placebo once daily before bedtime for 12 consecutive weeks.

Refer to the schedule of assessment of [Section 3.1.2](#) for a display of all assessments to be conducted. All visits are to be scheduled according to their time from the randomization visit (Visit 2).



3.1.2 Schedule of Assessment

Study Visits <sup>1)</sup>	Screening	Treatment Period							Follow-up
	V1	V2	V3	V4	V5	V6	V7	V8	V9
	Screen (Week -2)	Baseline (Week 0)	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Demographic (including height)	X								
Medical/Medication History	X								
Physical Examination	X	X		X		X		X	
Vital Signs and Body Weight	X	X	X	X	X	X	X	X	X
12-lead ECG	X							X	
Blood Sampling for serum chemistry, hematology, FPG, HbA1c, hCG, TSH, T3, and T4 <sup>2)</sup>	X	X		X		X		X	
Blood Sampling for zinc, insulin, adiponectin, C-peptide, leptin, glucagon, [CHP in a subset of subjects <sup>3)</sup>		X		X		X		X	
Urine Sampling for glucose, microalbumin, copper, and zinc		X		X		X		X	
Dispense and Review Daily Log	X	X	X	X	X	X	X	X	
Dispense and Review Medications		X	X	X	X	X	X	X	
Waist Circumference		X		X		X		X	
OGTT <sup>4)</sup>		X						X	
ADDQoL Questionnaire		X						X	
Review of Adverse Event and Concomitant Medication <sup>5)</sup>		X	X	X	X	X	X	X	X

- 1) Visits 3 to 8 have ±3 day visit window and Visit 9 has +7 day visit window.
- 2) Serum chemistry, hematology: Weeks -2, 0, 4, 8, and 12  
HbA1c: Weeks -2, 0, 4, 8, and 12  
FPG: Weeks 0, 4, 8, and 12  
TSH, T3, T4: Weeks 0 and 12  
Serum hCG (pregnancy): Weeks -2 and 12
- 3) CHP levels may be analyzed in a subset of subjects if residual serum and/or plasma samples are available after completion of protocol-required tests.
- 4) Subjects will be advised to maintain similar exercise and eating habits 3 days prior to the OGTT. Each subject will be instructed not to take his or her usual oral medications or insulin injection and food at least 12 hours before coming to the clinical site between 7:00 am and 8:30 am for an OGTT. Each subject will be allowed to drink only water during the 12-hour fasting period prior to the OGTT and advised not to consume any food. Initial blood will be drawn (15 min prior to OGTT) for serum chemical analysis. The subject will then consume a glucose solution (75 g), followed by one drop of blood drawn for glucose measurements with a glucometer at 0, 0.5, 1.0, 1.5, 2.0, 2.5 and 3 h in the clinical site.
- 5) Assess hypoglycemic & hyperglycemic episodes at Visits 2 to 8 only.

## 3.2 Study Population

### 3.2.1 Inclusion Criteria

To be enrolled in the study, a subject must meet all of the following criteria:

- 1) Males or females aged 18 or older.
- 2) Subjects diagnosed with type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria.
- 3) Subjects treated with stable doses of insulin and/or other hypoglycemic agent(s) for type 2 diabetes mellitus for at least 2 months prior to randomization.
- 4) Subjects whose fasting blood glucose levels are reasonably stable for at least 2 months prior to randomization and during the 2-week screening period. Stable glucose levels are defined based on the fact that the study subjects did not change the dose and/or type of insulin injection and/or other hypoglycemic agent(s) during the last 2 months and during the 2-week screening period to adjust blood glucose.
- 5) Subjects who have Hemoglobin A1c levels of 7.5 to 10.0 % at Screening.
- 6) Subjects whose BMI is 30 or above.
- 7) Subjects who can give written informed consent.

### 3.2.2 Exclusion Criteria

A subject must not be enrolled in the study if any of the following criteria are met:

- 1) Subjects who have any DM-related end-organ damages.
- 2) Subjects who have a history of diabetic ketoacidosis or hyperosmolar non-ketotic coma.
- 3) Subjects who have any disease likely to limit life span and/or increase risks of interventions such as:
  - Carotid B-mode ultrasound test results indicating clinically significant stenosis in the common carotid arteries requiring intervention by angioplasty or resection.
  - Cancer treatment in the past 5 years, with the exception of cancers which have been cured, and carry a good prognosis.
  - Infectious disease: HIV positivity, active tuberculosis, or pneumonia.
- 4) Subjects who have any of the following conditions related to cardiovascular disease:
  - Hospitalization for the treatment of heart disease in the past 12 months.
  - New York Heart Association Functional Class > 2.
  - Left Bundle branch block on ECG at Screening.
  - Third degree atrioventricular block on ECG at Screening.
  - Uncontrolled hypertension with average systolic blood pressure of > 160 mmHg or diastolic blood pressure > 95 mmHg at Screening and Baseline.
  - Pulse rate > 95 beats per minute at Screening and Baseline.
  - Stroke or transient ischemic attack in the past 12 months.
- 5) Subjects who have any of the following conditions related to gastrointestinal disease:
  - Chronic hepatitis or cirrhosis.
  - Episode of alcoholic hepatitis or alcoholic pancreatitis in the past 2 months.
  - Inflammatory bowel disease requiring treatment in the past 12 months.

- Significant abdominal surgery (e.g., gastrectomy, gastric bypass) in the past 2 months.
- 6) Subjects who have serum creatinine > 1.5 mg/dL for male or > 1.4 mg/dL for female.
- 7) Subjects who have chronic obstructive airway disease or asthma requiring daily therapy or home use oxygen.
- 8) Subjects who have hematocrit < 36.0% for male or < 33.0% for female.
- 9) Subjects who have any of the following conditions or behaviors likely to affect the conduct of the study:
  - Weight loss of > 10% in the past 6 months.
  - Unable to walk without assisted device.
  - Major psychiatric disorder which would impede conduct of the research.
  - Excessive alcohol intake (i.e., more than 2 drinks/day).
- 10) Subjects who take any of the following medications:
  - Psychoactive agents such as monoamine oxidase inhibitors and antidepressants (e.g., lithium, Prozac, Zoloft, Serzone, Paxil, Effexor).
  - Any other medications that may pose harm to the subject.
- 11) Female subjects who have a positive serum pregnancy test at Screening, plan a pregnancy during study period, or are breast feeding.
- 12) Female subjects who don't meet any of the following criteria:
  - Surgically sterile (i.e., have had bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 6 months before randomization.
  - Post-menopausal for at least 12 months prior to Screening.
  - If sexually active, they should use oral contraceptives, double barrier contraception (e.g., condom with spermicide), intrauterine device, or other methods approved by the Sponsor.

### 3.3 Sample Size Considerations

This is a Phase 2 clinical trial to evaluate safety and explore the potential efficacy of the study drug. Therefore, the number of subjects was not based on formal statistical power considerations. In this clinical trial, a total of 64 subjects was deemed sufficient and will be enrolled and randomly assigned to be administered with 1 of 3 dose levels of Cyclo-Z or placebo.

### 3.4 Randomization and Blinding

#### 3.4.1 Randomization

At Visit 2 (Week 0), subjects who meet the inclusion/exclusion criteria will be randomly assigned to receive placebo or 1 of 3 doses of Cyclo-Z in accordance with the randomization code, which will be generated by other Bio-statistics associate (BSA) at MediHelpline rather than the BSA in charge. Specifically, the subjects will be randomly assigned in a 1:1:1:1 ratio to the following:

- Dose A: Cyclo-Z containing 23 mg zinc plus 3 mg CHP – 16 subjects
- Dose B: Cyclo-Z containing 23 mg zinc plus 9 mg CHP – 16 subjects
- Dose C: Cyclo-Z containing 23 mg zinc plus 15 mg CHP – 16 subjects
- Dose D: Placebo – 16 subjects

### 3.4.2 Blinding

As this is a double-blind study, blinding of the drug contents from the subjects, Investigator, and other study personnel at each site is necessary. The subject will be assigned with an identification number at Visit 2 which will remain with the subject throughout the study.

A code-break document including the randomization code information will be retained by each site and can be opened, revealing the randomization information, for emergency purposes only. The Investigator should note that the occurrence of a SAE should not routinely precipitate immediate unblinding. An attempt to contact the Sponsor must be made prior to unblinding. If unblinding occurs, the study medication for the subject must be discontinued; a written explanation on the relevant form must be prepared immediately.

## 4. STUDY ENDPOINTS AND COVARIATES

### 4.1 Primary Endpoints

The primary clinical efficacy variables used to evaluate the efficacy of Cyclo-Z are:

- Change of HbA1c level from baseline at Week 12
- Change of body weight (BW) from baseline at Week 12

### 4.2 Secondary Endpoints

The secondary clinical efficacy variables used to evaluate the efficacy of Cyclo-Z are:

- Change of fasting plasma glucose (FPG) level from baseline at Week 12
- Proportion of subjects achieving HbA1c goal of < 7.0% at Week 12
- Proportion of subjects achieving HbA1c goal of < 6.5% at Week 12
- Change in waist circumference from baseline at Week 12
- Change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12
- Change of OGTT from baseline at Week 12
- Change of score in Audit of Diabetes-Dependent Quality of Life (ADDQoL) Questionnaire from baseline at Week 12

### 4.3 Exploratory Endpoints

In addition to the primary and secondary endpoints, the following exploratory efficacy variables will be separately evaluated for the change from baseline at Week 12:

- Thyroid Function Test: Thyroid Stimulating Hormone (TSH), Triiodothyronine (T3) and Thyroxine (T4)
- Serum Parameters: zinc, insulin, adiponectin, C-peptide, leptin and glucagon
- Urine Parameters: zinc, glucose, microalbumin and copper
- Three-hour-area-average Above Fasting Glucose Concentration (TAFGC)
- Body Mass Index (BMI)

#### 4.4 Safety Endpoints

The following safety parameters will be evaluated for the change from baseline assessment:

- Blood samples for complete laboratory evaluation
- ECG evaluation
- Physical examination
- Vital signs
- Adverse events
- Episodes of hypoglycemia and hyperglycemia

#### 4.5 Cyclo (His-pro) (CHP) Concentration Evaluation

In a subset of subjects where residual serum and/or plasma are available after completion of study-required tests, CHP levels in blood may be measured for the change from baseline.

### 5. HYPOTHESES

The primary objective is to assess the dose-dependent efficacy of Cyclo-Z for the treatment of subjects with obese type 2 diabetes. The hypothesis of this study is set as follows.

The dose-dependent efficacy of Cyclo-Z will be demonstrated by identifying statistically significant difference in the change of HbA1c level and BW from baseline at Week 12 in Dose A, B, C, and D using one-way analysis of variance (ANOVA) methods. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D.

$$H_0: \mu_A = \mu_B = \mu_C = \mu_D$$

$$H_1: \text{not } H_0$$

$\mu$ : the mean of the primary clinical efficacy variables by each of the four dose groups

### 6. DEFINITIONS

- **Baseline** is defined as the last non-missing measurement taken on Week 0.
- **Study day 1** is defined as the first IP dose date. For subjects who are randomized but not dosed after randomization, the study day 1 is defined as the date of randomization.
- **Study day** is defined as the number of days from study day 1.

Before study day 1: study day = (date of interest – date of study day 1)

On or after study day 1: study day = (date of interest – date of study day 1) + 1

Therefore, the day prior to study day 1 is -1.

- **Study drug exposure day** is defined as the number of days that subjects were on the study drug.
- **Age (years)** is calculated as follows, and is rounded down to an integer.

$$Age = \frac{Date\ of\ Informed\ Consent - Date\ of\ birth}{365.25}$$

- **Diabetes disease period (years)** is calculated as follows, and is rounded down to an integer.

$$Diabetes\ disease\ period = \frac{Date\ of\ Screening - Date\ of\ diagnosis^*}{365.25}$$

\*If the month and day of date of diagnosis are unknown, it will be converted into January, first day.

- **OGTT** of secondary endpoint is used glucose value at 2 hour after glucose intake.
- **TAFGC** is calculated as follows:

$$TAFGC = \frac{\sum_n [Glucose\ value\ at\ (n)\ hour\ in\ OGTT - Glucose\ value\ at\ 0\ hour\ in\ OGTT]}{6},$$

where  $n = 0.5, 1.0, 1.5, 2.0, 2.5, \text{ and } 3$

- **BMI (kg/m<sup>2</sup>)** is calculated as follows:

$$BMI = \frac{Body\ Weight\ (kg)}{Height\ (m) \times Height\ (m)}$$

- **Compliance (%)** is calculated as follows:

$$compliance = \frac{Number\ of\ capsules\ taken}{Number\ of\ capsules\ should\ be\ taken\ in\ principle^*} \times 100$$

\*By visit:  $Date\ of\ Visit(n) - Date\ of\ Visit(n - 1)$ , where  $n=3, 4, 5, 6, 7, \text{ and } 8$

Overall:  $\sum_n (Date\ of\ Visit(n) - Date\ of\ Visit(n - 1))$ , where  $n=3, 4, 5, 6, 7, \text{ and } 8$

## 7. ANALYSIS SUBSETS

This study is planned to analyze in analysis subsets of four groups: Full Analysis Set, Efficacy Analysis Set, Per Protocol Set, and Safety Analysis Set. For efficacy analysis, the Efficacy Analysis Set will be considered primarily and the Per Protocol Set will be considered as supportive. The Safety Analysis Set will be used in the safety analysis.

### 7.1 Full Analysis Set

The Full Analysis Set (FAS) includes all subjects who were randomized in the study. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Tabulations of subject

enrollment by site, subject disposition, analysis subsets, demographic and baseline characteristics including diabetes disease, past and present medical history, concomitant medication, and protocol deviations including major protocol deviations will utilize this analysis set.

## 7.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) will be used to carry out the efficacy analyses of efficacy endpoints, which is a subset of the FAS consisting of subjects who received at least one dose of study medication and who had baseline and any post-baseline efficacy data. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Analyses for efficacy endpoints will utilize this analysis set.

## 7.3 Per Protocol Set

All subjects valid for EAS who meet ALL the following criteria will be „valid per protocol“ (also called „valid for efficacy“):

- Complete at least 2 weeks of treatment after randomization.
- Have both baseline and at least 2 weeks of efficacy data.
- Subject did not have any significant violation after randomization.

Major protocol deviations that will potentially impact the primary analysis of efficacy endpoints at Week12 or violate GCP at site will be discussed and decided prior to the database lock and will be applied in per protocol analysis:

The following cases are excluded from the Per Protocol Set:

- Informed consent was not provided
- Subjects who were withdrawn/early terminated
- Subjects who have not met inclusion/exclusion criteria
- Subjects who received excluded concomitant medications
- Subjects who have major protocol deviations - all protocol deviations will be classified as major or minor under the discussion with Sponsor before database is locked.

Additional criteria maybe added prior to unblinding of the study database.

**The Per Protocol Set will be used to perform the sensitivity analysis on the primary, the secondary, and the exploratory efficacy endpoints.**

## 7.4 Safety Analysis Set

The Safety Analysis Set will consist of all randomized subjects who received at least one dose of study medication and had any post-randomization safety data collected will be included in the evaluation of safety. Analyses of demographic and baseline characteristics, safety endpoints and summary of study medication administration will utilize this analysis set.

## 8. INTERIM ANALYSIS

No interim analyses are planned for this Phase 2 study.

## 9. DATA SCREENING AND ACCPETANCE

### 9.1 General Principles

The objective of data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses. The Bio-statistics associate (BSA) who is in charge of this study will check errors of raw data prior to the beginning of data analysis.

### 9.2 Data Handling and Electronic Transfer of Data

After database is locked, a raw data validated by using Microsoft Structured Query Language (MsSQL) will be directly accessed using SAS Open Database Connectivity (ODBC) Driver. The raw data needed for analysis will be transferred from Database Management System (DBMS) to standard folder to store the raw data on the server via SAS ODBC, and the analysis dataset will be created in „DATASET“ folder. The analysis dataset will be generated using SAS software version 9.4 according to analysis dataset specification created in accordance with this SAP.

### 9.3 Handling of Missing and Incomplete Data

If subjects either discontinues from the clinical trial or the outcome measurement at any point is missing post-baseline, then the missing data will be imputed from the last measured outcome value using the Last Observation Carried Forward (LOCF) method.

#### 9.3.1 Missing and Incomplete Dates

Missing or incomplete dates will be listed as it is in any listings.

Incomplete start date of an adverse event or concomitant medication taken will be handled by following rule:

Start Date	Missing	Imputation	Exception
Adverse Event Concomitant Medication	Day	01	Default to Study Day 1 if an AE starts at the same year and month as Study Day 1 and the flag indicates that the AE started on or after the first dose on the AE CRF
	Day/Month	01JAN	Default to Study Day 1 if an AE started at the same year as Study Day 1 and the flag indicates that the AE started on or after the first dose on the AE CRF
	Day/Month/Year	No Imputation	



### 9.3.2 Missing Baseline Evaluation

Missing baseline will not be imputed.

### 9.3.3 Missing Post-Baseline Evaluation

Primary analysis of continuous efficacy endpoints will be analyzed based on observed data without imputation.

In the sensitivity analysis of primary and the secondary efficacy endpoints, missing continuous efficacy endpoints will be handled using the LOCF method.

In the LOCF method, post-baseline missing continuous endpoints will be imputed using the last observed value including baseline value. For example, if subject has all of the post-baseline values as missing, then all of the post-baseline values will be imputed using the observed baseline value.

### 9.3.4 Handling of Repeated Laboratory Test Results

Repeated laboratory test data will be handled after identifying the reason. If it is due to a test error, then the last value of the visit will be used, and if a clinical opinion is required, then the team will request the clinician's opinion and will decide what value to use.

### 9.4 Handling of Early Termination

In order to analyze and summarize the data consistently, the last visit performed for Early Termination will be mapped to their closest to scheduled visit within the analysis dataset.

For example, if a subject completed efficacy measurement at Week 0, then the subject got early terminated from the study 4 weeks later and completed efficacy measurement, then the efficacy measurement for ET will be mapped to Week 4 visit.

Example #1:

Before:

<b>Week 0 (02FEB2017)</b>	<b>ET (02MAR2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done

After:

<b>Week 0 (02FEB2017)</b>	<b>Week 4 (02MAR2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done

Note: Week 2 to Week 12 have  $\pm 3$  day visit window

Example #2:

Before:

<b>Week 0 (02FEB2017)</b>	<b>ET (05MAR2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done

After:

<b>Week 0 (02FEB2017)</b>	<b>Week 4 (05MAR2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done

Note: Week 2 to Week 12 have ± 3 day visit window

For example, if a subject completed efficacy measurement at Weeks 0, 4, 8 then the subject got early terminated from the study 4 weeks later after Week 8 and completed efficacy measurement, and then the efficacy measurement for ET will be mapped to Week 12 visit.

Example #3:

Before:

<b>Week 0 (29MAR2017)</b>	<b>Week 4 (26APR2017)</b>	<b>Week 8 (24MAY2017)</b>	<b>ET (21JUN2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done	Efficacy Measurement – Done	Efficacy Measurement – Done

After:

<b>Week 0 (29MAR2017)</b>	<b>Week 4 (26APR2017)</b>	<b>Week 8 (24MAY2017)</b>	<b>Week 12 (21JUN2017)</b>
Efficacy Measurement – Done	Efficacy Measurement – Done	Efficacy Measurement – Done	Efficacy Measurement – Done

Note: Week 2 to Week 12 have ± 3 day visit window

Each case will be discussed and decided with the study team and will be documented in the analysis dataset specification.

### 9.5 Outliers Detection

Histograms or raw data review will be examined to identify outliers in any of the continuous variables used in the analyses. Unexpected and/or unexplained values in categorical data will be identified by utilizing frequency tables.

Outliers due to data entry errors will be corrected by the study team before the database lock. The validity of any questionable values or outliers will be confirmed. Outliers or any questionable values with confirmed validity will be included in the analyses. However, ad-hoc sensitivity analyses may be conducted to evaluate the influence of extreme values in the data. If it is deemed necessary after the team reviews the output from the planned analyses after the database lock, post-hoc analyses excluding subjects with outliers may be performed.

## 9.6 Bias Detection

Randomization and blinding are performed for avoiding bias in this phase 2 study. Major protocol deviations will be listed and or/tabulated in the clinical study report (CSR). Any breaking of the blind for individual subjects prior to unblinding of the study will be documented in the CSR. The timing of and reasons for premature withdrawal from treatment and from study will be tabulated and /or listed.

## 9.7 Distributional Characteristics

Continuous endpoints of change from baseline value will be analyzed under normality assumption. If they deviate appreciably from normality, then appropriate non-parametric alternatives will be considered.

## 9.8 Validation of Statistical Analyses

The procedure for the validation of the analysis result is as follows:

- 1) Self-check: The BSA in charge will check for oneself that the SAS program code, output, execution log, etc. are written correctly.
- 2) Double programming and the review: The BSA in charge and other BSA will write SAS program code independently, and the Bio-statistics manager (BSM; Reviewer) will compare the outputs such as table, graph, listing that are printed by the SAS program code.
- 3) Source code check: The BSM will check the written source code visually, and will check whether it is properly processed according to its purpose.
- 4) Table/Graph: The BSM will check the values displayed in tables and graphs.
- 5) Listing/Raw data: The BSM will check whether the raw data and listing are the same or not.

# 10. STATISTICAL ANALYSES

## 10.1 General Principles

Statistical analysis will be conducted after database is locked and performed using SAS software version 9.4 according to this SAP. If statistical analysis methods are changed, it will be described in the final clinical study report.

Continuous variables will be summarized with means, standard deviations, medians, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimums, and maximums. Categorical variables will be summarized with counts and percentages. P-values less than 0.05 will be considered statistically significant. No adjustments for multiple comparison will be made to the result presented in this study because this is a phase 2 clinical trial and it is not formally powered with statistical algorithms.

## 10.2 Subject Disposition

The disposition of all randomized patients will be tabulated by randomized treatment group. The numbers of all patients classified as follows will be summarized with count, percentage and flow chart by site and treatment group.

- All patients who enrolled into the study
- Patients who were randomized
- Patients who were treated
- Patients who were completed
- Prematurely withdrawn
- The reasons for premature withdrawal

## 10.3 Protocol Deviations

- All protocol deviations occurred during this study will be summarized by treatment group. Subjects who have protocol deviations will be categorized as follows;
  - 1) Subjects who have visits outside window
  - 2) Subjects who have not met inclusion criteria or met exclusion criteria but were entered into the study
  - 3) Subjects who received an excluded concomitant medications/treatment
  - 4) Subjects who have other protocol deviations
- Individual patients with these protocol deviations will be listed by site.

## 10.4 Demographic and Baseline Characteristics

Demographic characteristics, medical history, medication history, extent of exposure, and efficacy variables at baseline will be summarized using descriptive statistics by randomized treatment group and overall study population using FAS and Safety Analysis Set. Continuous variables will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum and maximum. Categorical variables will be summarized with count (number of subjects and/or number of events) and percentage. Because, in theory, the goal of randomization is to balance out the subject characteristics, statistical tests are not planned for these variables.

### 10.4.1 Demographic Characteristics

- Sex (Male, Female)
- Age
- Ethnicity (Hispanic, Non-Hispanic)
- Race (Black or African American, Native Hawaiian or other Pacific Islander, Native American Indian or Native Alaskan, Asian, White, Other)
- Height

#### 10.4.2 Medical History

- Type of Diabetes (Type I Diabetes, Type II Diabetes, Gestational Diabetes)
- Diabetes disease period
- Past medical history status (Yes, No) and past medical history classified by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (Medical Dictionary for Regulatory Activities) version 20.0.
- Present medical history status (Yes, No) and present medical history classified by SOC and PT according to MedDRA version 20.0

#### 10.4.3 Concomitant Medications

- Status (Yes, No) of concomitant medications and concomitant medications classified by Level1 and Level2 according to Anatomical Therapeutic Chemical (ATC) code WHODRUG version 2017 at V1 (screening)

#### 10.4.4 Efficacy Variables at Baseline

- HbA1c
- Body Weight (BW)
- FPG level
- Waist Circumference
- Mean value of postprandial (2 hours after dinner) blood glucose level
- OGTT
- ADDQoL questionnaire scores
- Thyroid Function Test: TSH, T3, and T4
- Serum parameters: zinc, insulin, adiponectin, C-peptide, leptin, and glucagon
- Urine parameters: zinc, glucose, microalbumin, and copper
- TAFGC
- BMI

#### 10.5 Efficacy Analyses

The analyses of efficacy endpoints will utilize EAS. Subjects will be analyzed according to their randomized treatment group regardless of the actual treatment received during the study. Per protocol analyses of the primary, secondary, and exploratory endpoints will utilize the Per Protocol Set.

Detailed primary analysis methods, sensitivity analyses are summarized in the table below.

<b>Endpoints</b>	<b>Primary Analysis and Analysis Method</b>	<b>Sensitivity Analysis at Week 12</b>
<b>Primary Endpoints</b>		
Change of HbA1c level from baseline at Week 12 Change of BW from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
<b>Secondary Endpoints</b>		
Change of FPG level from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
Proportion of subjects achieving HbA1c goal of < 7.0% at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: Chi-square test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using chi-square test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
Proportion of subjects achieving HbA1c goal of < 6.5% at Week 12	Same as above	Same as above
Change in waist circumference from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
Change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12	Same as above	Same as above
Change of OGTT from baseline at Week 12	Same as above	Same as above
Change of score in ADDQoL questionnaire from baseline at Week 12	Same as above	Same as above

Endpoints	Primary Analysis and Analysis Method	Sensitivity Analysis at Week 12
<b>Exploratory Endpoints</b>		
Change of following variables from baseline at Week 12: <u>Thyroid Function Test</u> : TSH, T3, and T4 <u>Serum Parameters</u> : zinc, insulin, adiponectin, C-peptide, leptin, and glucagon <u>Urine Parameters</u> : zinc, glucose, microalbumin, and copper <u>TAFGC</u> <u>BMI</u>	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12

### 10.5.1 Primary Efficacy Analyses

- The change of HbA1c level from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of HbA1c level from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- The change of BW from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of BW from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- Sensitivity analysis described below will be performed for the primary endpoints at Week 12:
  1. Summary statistics and ANOVA model for continuous endpoints using imputed data by LOCF, EAS.
  2. Primary summary and analysis method based on Per Protocol Set.

### 10.5.2 Secondary Efficacy Analyses

- The change of FPG level from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of FPG level from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- The proportion of subjects achieving HbA1c goal of < 7.0% at Week 12 will be summarized with count and percentage, overall and by each of the four groups, separately. The proportion of subjects achieving HbA1c goal of < 7.0% at Week 12 will be compared for the experimental groups versus the control group using chi-square test method. In a case when the expected cell frequencies are less than 5 in >20%, Fisher's exact test will be used.
- The proportion of subjects achieving HbA1c goal of < 6.5% at Week 12 will be summarized with count and percentage, overall and by each of the four groups, separately. The proportion of subjects achieving HbA1c goal of < 6.5% at Week 12 will be compared for the experimental groups versus the control group using chi-square test method. In a case when the expected cell frequencies are less than 5 in >20%, Fisher's exact test will be used.
- The change in waist circumference from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change in waist circumference from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- The change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically,



all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.

- The change of OGTT from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of OGTT from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- The change of score in ADDQoL questionnaire from baseline at Week 12 will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the change of score in ADDQoL questionnaire from baseline at Week 12 between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.
- Sensitivity analysis described below will be performed for the secondary endpoints at Week 12:
  1. Summary statistics and ANOVA model for continuous endpoints using imputed data by LOCF, EAS.
  2. Primary summary and analysis method based on Per Protocol Set.

### 10.5.3 Exploratory Efficacy Analyses

The exploratory efficacy variables will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum, overall and by each of the four groups, separately. To identify statistically significant difference in the exploratory efficacy variables between the four groups, one-way ANOVA will be performed. The tests between the experimental groups and the control group will be performed using Dunnett's test. If the change variables are markedly non-normally distributed then Kruskal-Wallis test and Wilcoxon rank-sum test will be used respectively. Specifically, all three experimental groups will be compared to the control group on the change: Dose A vs. D, B vs. D, and C vs. D. Also, to identify statistical significant difference between baseline and Week 12, one-sample t-test (paired t-test) or Wilcoxon signed-rank test will be performed within each of the four groups.

- Thyroid Function Test: TSH, T3, and T4
  - Serum Parameters: zinc, insulin, adiponectin, C-peptide, leptin, and glucagon
  - Urine Parameters: zinc, glucose, microalbumin, and copper
  - TAFGC
  - BMI
- Sensitivity analysis described below will be performed for the exploratory endpoints at Week 12:
1. Primary summary and analysis method based on Per Protocol Set.

## 10.6 Safety Analyses

Safety analysis will be performed based on data of safety analysis set. Safety variables will be summarized with descriptive statistics, overall and by each of the four groups, separately. Continuous safety variables will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum. Categorical safety variables will be summarized with count and percentage.

**No statistical testing comparing treatment groups will be performed in the safety analyses.**

### 10.6.1 Adverse Events

- All adverse events (AEs) in CRF will be classified by SOC and PT according to MedDRA version 20.0.
- A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened on or after the first treatment dose. AEs recorded prior to the first application of study treatment will be considered non-treatment-emergent. AEs with insufficient date or time information to determine whether or not they were treatment-emergent will be considered treatment-emergent.
- All reported AEs (treatment-emergent or not) will be listed. Only TEAEs will be summarized.
  - (1) TEAEs will be summarized with the number of subjects who have AEs, incidence rate of AEs, and the number of AEs by categorizing as follows;
    - ① AE/ADR\* (Adverse event/Adverse drug reaction)  
\*TEAEs which have the relationship to investigational product as 'Definite', 'Probable', and 'Possible' are regarded as Drug-Related Adverse Events (ADR).
    - ② SAE/SADR (Serious adverse event/Serious adverse drug reaction)
  - (2) TEAEs will also be summarized with the number of subjects who have AEs, incidence rate of AEs, the number of AEs, and its percentage by categorizing as follows.
    - ① Outcome
      - Recovered or Resolved
      - Recovering or Resolving
      - Recovered or Resolved with Sequelae
      - Not Recovered or Not Resolved

- Death Related to Adverse Event
  - Unknown
  - ② Severity
    - Mild
    - Moderate
    - Severe
  - ③ Relationship to Investigational Product (IP)
    - Definite
    - Probable
    - Possible
    - Not Likely
    - Not Related
  - ④ Action Taken Regarding IP
    - None
    - Reduced
    - Increased
    - Interrupted
    - Discontinued
  - ⑤ Treatment Required
    - Yes
    - No
  - ⑥ Seriousness
    - Is life-threatening
    - Requires in-patient hospitalization or prolongation of existing hospitalization
    - Results in persistent or significant disability or incapacity
    - Is a congenital anomaly or birth defect
    - Is an important medical event
    - Results in death
- Episodes of hypoglycemia and hyperglycemia (V2-V8)
    - (1) Hypoglycemia occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.
    - (2) Hyperglycemia occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.
    - (3) Sponsor defined Hypoglycemia (blood glucose  $\leq 70$  mg/dL) occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.

- (4) Sponsor defined Hyperglycemia (blood glucose  $\geq$  180 mg/dL) occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.

#### 10.6.2 Laboratory Test Results

- Laboratory tests are:
  - Hematology: RBC, WBC, Neutrophil count, Lymphocyte count, Monocyte count, Eosinophil count, Basophil count, Hematocrit, Hemoglobin, Platelets, MCH, MCHC, MCV, and RDW
  - Chemistry: ALT, Albumin, Alkaline phosphatase, AST, Total Bilirubin, BUN, Calcium, Bicarbonate, Chloride, Creatinine, Potassium, Total Protein, Sodium, and Glucose
- Laboratory test results will be collected at V1, V2, V4, V6, and V8. These variables will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum by each treatment group and by each visit separately.
- Normality of laboratory test results [Normal, Abnormal (CS, NCS)] will be summarized with count (number of subjects) and percentage by each treatment group and by each visit separately.

#### 10.6.3 Vital Signs

- Vital signs [Sitting blood pressure (systolic, diastolic), Heart rate, Breathing, and Temperature] will be collected at V1, V2, V3, V4, V5, V6, V7, V8, and V9. These variables will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum and maximum by each treatment group and by each visit separately.

#### 10.6.4 Physical Examination and 12-lead ECG

- Result of physical examination (General Appearance, Head-Ears-Eyes-Nose-Throat, Neck, Heart, Lungs, Abdomen, Lymph Nodes, Genitourinary, Extremities, Neurological, Skin, Musculoskeletal, and Others) will be collected at V1, V2, V4, V6, and V8. These results (Normal, Abnormal) will be summarized with count (number of subjects) and percentage by each treatment group and by each visit separately.
- Result of 12-lead ECG will be collected at V1 and V8. This result [Normal, Abnormal (CS, NCS)] will be summarized with count and percentage by each treatment group and by each visit separately.

#### 10.6.5 Exposure to IP

- Study drug exposure day will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum by each treatment group and by each visit separately.

- Number of Capsules taken will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum by each treatment group and by each visit separately.
- Compliance will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum by each treatment group and by each visit separately.

#### 10.6.6 Concomitant Medication Use

- Concomitant medications status (Yes, No) collected at V2-V9 will be summarized with count and percentage by each treatment group separately. Concomitant medications classified by Level1 and Level2 according to ATC code WHODRUG version 2017 will be also summarized.

#### 10.7 CHP Concentration Analysis

Levels of CHP assessed in blood for a subset of subjects if there are residual serum and/or plasma after completion of protocol-required tests will be summarized with mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum.

**No statistical tests are planned for these data.**

#### 10.8 Subgroup Analysis

To explore the robustness of efficacy signal, primary, secondary, and exploratory efficacy endpoints may also be analyzed separately by excluding potential outliers.

#### 10.9 Post-hoc Analysis

To understand the data better for future study design, post-hoc analyses may also be performed separately.

### 11. REPORTING CONVENTIONS

All results of analysis will be reported in table or figure format to assist the understanding for the study results. The descriptive summary statistics for continuous variables will be presented in the number of subjects (n), mean, standard deviation, median, 25<sup>th</sup> & 75<sup>th</sup> percentiles, minimum, and maximum and the descriptive summary statistics for categorical variables will be given as frequencies, percentages.

The number of decimal places presented for each statistic will be as follows:

- Mean, median, 25<sup>th</sup> percentile, 75<sup>th</sup> percentile: one more than the number of decimal places recorded x
- Standard deviation: two more than the number of decimal places recorded x
- Minimum and maximum: equal to the number of decimal places recorded
- Percentage: reported to one decimal place using rounding off
- P-value: reported to four decimal places and if p-values smaller than 0.0001 will be written as „<0.0001“.

All dates will be displayed in DDMMYYYY format (for example, 11JAN2015).

Data for individual subjects will be presented in data listings.

## 12. ADJUSTED STATISTICAL ANALYSIS METHOD

Not applicable.

## 13. CHANGES IN THE STATISTICAL ANALYSIS FROM THE PROTOCOL

[Section 4.3](#) Two exploratory endpoints have been added. The endpoints are as follows:

- Change in TAFGC from baseline at Week 12
- Change in BMI from baseline at Week 12

[Section 6](#) New definitions have been added for Baseline, Study Day. The definitions are as follows:

**Baseline** is defined as the last non-missing measurement taken on Week 0.

**Study day 1** is defined as the first IP dose date. For subjects who are randomized but not dosed after randomization, the study day 1 is defined as the date of randomization.

**Study day** is defined as the number of days from study day 1.

Before study day 1:  $\text{study day} = (\text{date of interest} - \text{date of study day 1})$

On or after study day 1:  $\text{study day} = (\text{date of interest} - \text{date of study day 1}) + 1$

Therefore, the day prior to study day 1 is -1.

[Section 7.1](#) Full Analysis Set has been added. The definition of FAS is as follows:

The Full Analysis Set (FAS) includes all subjects who were randomized in the study. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Tabulations of subject enrollment by site, analysis subsets, demographic and baseline characteristics including diabetes disease, past and present medical history, concomitant medication, subject disposition, and major protocol deviations will utilize this analysis set.

[Section 7.2](#) Efficacy Analysis Set has been replaced with Intent-to-Treat Set. The updated definition of EAS is as follows:

The Efficacy Analysis Set (EAS) will be used to carry out the efficacy analyses of efficacy endpoints, which is a subset of the FAS consisting of subjects who received at least one dose of study medication and who had baseline and any post-baseline efficacy data. Subjects will be analyzed according to their randomized treatment, regardless of the treatment received. Analyses for efficacy endpoints will utilize this analysis set.

[Section 9.3](#) Handling of missing, incomplete data, and repeated laboratory test data has been added in detail. The details are as follows:

Only participants whose efficacy variable were measured least once after baseline. If participants either discontinues from the clinical trial or the outcome measurement at any point is missing, then the missing data will be imputed from the last measured outcome value using the Last Observation Carried Forward (LOCF) method.

If repeated laboratory test data collected is due to a test error, then the last value of the visit will be used, and if a clinical opinion is required, then it will be used one value determined under discussion.

No imputation methods are planned for safety analysis.

[Section 9.4](#) Handling of Early Termination has been added in detail. The details are as follows:

In order to analyze and summarize the data consistently, the last visit performed for Early Termination will be mapped to their closest to scheduled visit within the analysis dataset. See Section 9.4 of this SAP to see more examples in detail.

[Section 10.5](#) Efficacy Analyses. The detailed primary analysis methods, sensitivity analyses are added and summarized in the table below.

Endpoint	Primary Analysis and Analysis Method	Sensitivity Analysis at Week 12
<b>Primary Endpoints</b>		
Change of HbA1c level from baseline at Week 12 Change of BW from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
<b>Secondary Endpoints</b>		
Change of FPG level from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
Proportion of subjects achieving HbA1c goal of < 7.0% at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: Chi-square test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using chi-square test 2. <u>Per Protocol Set</u> : Same as

Endpoint	Primary Analysis and Analysis Method	Sensitivity Analysis at Week 12
		primary summary and analysis method at Week 12
Proportion of subjects achieving HbA1c goal of < 6.5% at Week 12	Same as above	Same as above
Change in waist circumference from baseline at Week 12	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>LOCF, EAS</u> : Summary statistics and analyze using an ANOVA model and Dunnett's test, and paired t-test 2. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12
Change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12	Same as above	Same as above
Change of OGTT from baseline at Week 12	Same as above	Same as above
Change of score in ADDQoL questionnaire from baseline at Week 12	Same as above	Same as above
<b>Exploratory Endpoints</b>		
Change of following variables from baseline at Week 12: <u>Thyroid Function Test</u> : TSH, T3, and T4 <u>Serum Parameters</u> : zinc, insulin, adiponectin, C-peptide, leptin, and glucagon <u>Urine Parameters</u> : zinc, glucose, microalbumin, and copper <u>TAFGC</u> <u>BMI</u>	1. EAS: Summary statistics by visit using observed data 2. EAS: ANOVA model and Dunnett's test, and paired t-test	1. <u>Per Protocol Set</u> : Same as primary summary and analysis method at Week 12

[Section 10.6.1](#) New definition of Hypoglycemia and Hypoglycemia have been added in detail. The details are as follows:

- (1) Sponsor defined Hypoglycemia (blood glucose  $\leq$  70 mg/dL) occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.



- (2) Sponsor defined Hyperglycemia (blood glucose  $\geq$  180 mg/dL) occurred after previous visit will be summarized with the number of subjects who are occurred episode and the count of episode by each visit separately.

[Section 10.8](#) Subgroup Analysis has been added. The details are as follows:

To explore the robustness of efficacy signal, primary, secondary, and exploratory efficacy endpoints may also be analyzed separately by excluding potential outliers.

[Section 10.9](#) Post-hoc Analysis has been added. The details are as follows:

To understand the data better for future study design, post-hoc analyses may also be performed separately.

## 14. REFERENCES

Clinical Study Protocol “A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study to Evaluate the Efficacy and Safety of Cyclo-Z in Patients with Obese Type 2 Diabetes”, Version 2.4, December 9, 2016