

## Clinical Study Protocol

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Protocol Title: 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

Protocol Number: NMP-CYZ-P2-001

Date of Protocol/Version: December 9, 2016 / Ver 2.4  
(Previous: May 23, 2016 / Ver 2.3)

Product: Cyclo-Z

IND No.: 61,897

Study Phase: 2

Sponsor: NovMetaPharma Co., Ltd.

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I have carefully read the attached protocol entitled “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” dated December 9, 2016 and agree to its terms including principles of disclosure and confidentiality.

I agree to submit this protocol to the Institutional Review Board to obtain its approval prior to initiation of the study.

I also agree to comply with the International Conference on Harmonization (ICH) Tripartite Guidelines on Good Clinical Practice, and applicable regulations/guidelines set forth in the Code of Federal Regulations Title 21, Parts 11, 50, 54, 56, and 312.

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Signature

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Name of Principal Investigator

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Date

### Protocol Version and Amendment Tracking

<b>Version Number/Amendment</b>	<b>Approval Date</b>
1.0	October 2, 2013
2.0	January 8, 2015
2.1	February 27, 2015
2.2	April 29, 2016
2.3	May 23, 2016
2.4	December 9, 2016

## Protocol Synopsis

<b>Name of Sponsor/Company:</b> NovMetaPharma Co., Ltd.	
<b>Study Product:</b> Cyclo-Z	
Protocol Number	NMP-CYZ-P2-001
Indication	Obese Type 2 Diabetes
Protocol Title	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
Study Development Phase	2
Planned Number of Subjects	Total of 64 subjects (4 groups)
Objectives	<p>The primary objective is to assess the dose-dependent efficacy of Cyclo-Z for the treatment of subjects with obese type 2 diabetes.</p> <p>The secondary objective is to assess the safety of Cyclo-Z in the treatment of subjects with obese type 2 diabetes.</p>
Clinical Endpoints	<p>The primary clinical efficacy variables used to evaluate the efficacy of Cyclo-Z are 1) the change of HbA1c level from baseline at Week 12 and 2) the change of body weight (BW) from baseline at Week 12.</p> <p>The secondary clinical efficacy variables used to evaluate the efficacy of Cyclo-Z are:</p> <ul style="list-style-type: none"> <li>• Change of fasting plasma glucose (FPG) level from baseline at Week 12</li> <li>• Proportion of subjects achieving HbA1c goal of &lt;7.0% at Week 12</li> <li>• Proportion of subjects achieving HbA1c goal of &lt;6.5% at Week 12</li> <li>• Change in waist circumference from baseline at Week 12</li> <li>• Change of postprandial (2 hours after dinner) blood glucose level from baseline at Week 12</li> <li>• Change of OGTT from baseline at Week 12</li> <li>• Change of score in Audit of Diabetes-Dependent Quality of Life (ADDQoL) Questionnaire from baseline at Week 12</li> </ul> <p>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:</p> <ul style="list-style-type: none"> <li>• Thyroid Function Test (TSH, T3, and T4)</li> <li>• Serum Parameters: zinc, insulin, adiponectin, C-peptide, leptin, glucagon</li> <li>• Urine Parameters: zinc, glucose, microalbumin, copper</li> </ul> <p>The safety variables include:</p> <ul style="list-style-type: none"> <li>• Blood samples for complete laboratory evaluation</li> <li>• ECG evaluation</li> <li>• Physical examination</li> <li>• Vital signs</li> <li>• Adverse events</li> <li>• Episodes of hypoglycemia and hyperglycemia</li> </ul>

<b>Name of Sponsor/Company:</b> NovMetaPharma Co., Ltd.	
<b>Study Product:</b> Cyclo-Z	
Protocol Number	NMP-CYZ-P2-001
Indication	Obese Type 2 Diabetes
	In a subset of subjects, Cyclic dipeptide (his-pro) (CHP) levels in blood may be measured.
Study Design	<p>This is a double-blind, randomized, placebo-controlled, parallel-group comparison study to evaluate the efficacy and safety of Cyclo-Z for the treatment of subjects with obese type 2 diabetes.</p> <p>The study will consist of 3 phases:</p> <ul style="list-style-type: none"> <li>• Screening phase (2 weeks)</li> <li>• Treatment phase (12 weeks)</li> <li>• Follow-up phase (2 weeks)</li> </ul> <p>Following a 2-week screening period, subjects who meet all inclusion and exclusion criteria will be randomly assigned into one of the following treatment arms:</p> <ul style="list-style-type: none"> <li>• Dose A: Cyclo-Z containing 23 mg zinc plus 3 mg CHP – 16 subjects</li> <li>• Dose B: Cyclo-Z containing 23 mg zinc plus 9 mg CHP – 16 subjects</li> <li>• Dose C: Cyclo-Z containing 23 mg zinc plus 15 mg CHP – 16 subjects</li> <li>• Dose D: Placebo – 16 subjects</li> </ul> <p>The assigned dose will be orally administered to subjects once a day before bedtime for 12 consecutive weeks. After the randomization at Week 0 (Visit 2), subjects will visit their respective trial sites at Weeks 2, 4, 6, 8, 10, 12, and 14 (Visits 3, 4, 5, 6, 7, 8, and 9).</p>
Inclusion/ Exclusion Criteria	<p>Eligibility will be determined based upon medical record review, physical examination, questionnaire and ECG results. All study subjects must meet the eligibility criteria based on the following inclusion and exclusion criteria:</p> <p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Males or females aged 18 or older.</li> <li>2. Subjects diagnosed with type 2 diabetes mellitus according to the American Diabetes Association (ADA) criteria.</li> <li>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.</li> <li>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.</li> <li>5. Subjects who have Hemoglobin A1c levels of 7.5 to 10.0 % at Screening.</li> <li>6. Subjects whose BMI is 30 or above.</li> <li>7. Subjects who can give written informed consent.</li> </ol> <p><b>Exclusion criteria:</b></p> <ol style="list-style-type: none"> <li>1. Subjects who have any DM-related end-organ damages.</li> <li>2. Subjects who have a history of diabetic ketoacidosis or hyperosmolar non-ketotic</li> </ol>

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	<p>coma.</p> <ol style="list-style-type: none"> <li>3. Subjects who have any disease likely to limit life span and/or increase risks of interventions such as: <ul style="list-style-type: none"> <li>• Carotid B-mode ultrasound test results indicating clinically significant stenosis in the common carotid arteries requiring intervention by angioplasty or resection.</li> <li>• Cancer treatment in the past 5 years, with the exception of cancers which have been cured, and carry a good prognosis.</li> <li>• Infectious disease: HIV positivity, active tuberculosis, or pneumonia.</li> </ul> </li> <li>4. Subjects who have any of the following conditions related to cardiovascular disease: <ul style="list-style-type: none"> <li>• Hospitalization for the treatment of heart disease in the past 12 months.</li> <li>• New York Heart Association Functional Class &gt; 2.</li> <li>• Left Bundle branch block on ECG at Screening.</li> <li>• Third degree atrioventricular block on ECG at Screening.</li> <li>• Uncontrolled hypertension with average systolic blood pressure of <math>\geq 160</math> mmHg or diastolic blood pressure <math>\geq 95</math> mmHg at Screening and Baseline.</li> <li>• Pulse rate <math>\geq 95</math> beats per minute at Screening and Baseline.</li> <li>• Stroke or transient ischemic attack in the past 12 months.</li> </ul> </li> <li>5. Subjects who have any of the following conditions related to gastrointestinal disease: <ul style="list-style-type: none"> <li>• Chronic hepatitis or cirrhosis.</li> <li>• Episode of alcoholic hepatitis or alcoholic pancreatitis in the past 2 months.</li> <li>• Inflammatory bowel disease requiring treatment in the past 12 months.</li> <li>• Significant abdominal surgery (e.g., gastrectomy, gastric bypass) in the past 2 months.</li> </ul> </li> <li>6. Subjects who have serum creatinine <math>\geq 1.5</math> mg/dL for male or <math>\geq 1.4</math> mg/dL for female.</li> <li>7. Subjects who have chronic obstructive airway disease or asthma requiring daily therapy or home use oxygen.</li> <li>8. Subjects who have hematocrit &lt; 36.0% for male or &lt; 33.0% for female.</li> <li>9. Subjects who have any of the following conditions or behaviors likely to affect the conduct of the study: <ul style="list-style-type: none"> <li>• Weight loss of &gt; 10% in the past 6 months.</li> <li>• Unable to walk without assisted device.</li> <li>• Major psychiatric disorder which would impede conduct of the research.</li> <li>• Excessive alcohol intake (i.e., more than 2 drinks/day).</li> </ul> </li> <li>10. Subjects who take any of the following medications: <ul style="list-style-type: none"> <li>• Psychoactive agents such as monoamine oxidase inhibitors and antidepressants (e.g., lithium, Prozac, Zoloft, Serzone, Paxil, Effexor).</li> <li>• Any other medications that may pose harm to the subject.</li> </ul> </li> <li>11. Female subjects who have a positive serum pregnancy test at Screening, plan a pregnancy during study period, or are breast feeding.</li> <li>12. Female subjects who don't meet any of the following criteria: <ul style="list-style-type: none"> <li>• Surgically sterile (i.e., have had bilateral tubal ligation, hysterectomy, or</li> </ul> </li> </ol>

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	<p>bilateral oophorectomy) at least 6 months before randomization.</p> <ul style="list-style-type: none"> <li>• Post-menopausal for at least 12 months prior to Screening.</li> <li>• 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.</li> </ul>
Statistical Analysis	<p>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.</p> <p>The co-primary variables, the reduction in HbA1c levels from baseline at Week 12 and the reduction of body weight (BW) from baseline at Week 12, will be analyzed using (ANOVA) methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.</p> <p>The continuous secondary efficacy variables will be analyzed with ANOVA or Wilcoxon rank sum tests, as appropriate. The categorical secondary efficacy variables will be analyzed with chi-square tests or Fisher's exact tests, as appropriate.</p> <p>The continuous exploratory efficacy variables will be analyzed with ANOVA or Wilcoxon rank sum tests, as appropriate. The categorical exploratory efficacy variables will be analyzed with chi-square tests or Fisher's exact tests, as appropriate.</p> <p>Safety variables will be summarized descriptively, by treatment group and visit. No formal statistical testing will be completed on the safety variables.</p>

### Schedule of Assessments

*Note: A subject needs to visit the clinical site before breakfast for all study visits except the safety follow-up visit.*

Study Visits <sup>1)</sup>	Screening	Treatment Period							Follow-up
	V1	V2	V3	V4	V5	V6	V7	V8	V9
	Screen (Wk -2)	Baseline (Wk 0)	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 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) See Appendix 1.
- 5) Assess hypoglycemic & hyperglycemic episodes at Visits 2 to 8 only.



## List of Abbreviations

<b>Abbreviation</b>	<b>Definition</b>
AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
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
DM	Diabetes Mellitus
DPP	Dipeptidyl Peptidase
DW	Distilled Water
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
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
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Insulin Degrading Enzyme
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent to Treat
NIDDM	Non-insulin-dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PP	Per-Protocol
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
SOP	Standard Operating Procedure
TAFGC	Three-hour-area-average Above Fasting Glucose Concentration

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## 1. Introduction

### 1.1 Type 2 Diabetes / Non-insulin-dependent Diabetes Mellitus (NIDDM)

Approximately 29.1 million people in the United States are afflicted with Type 2 diabetes or non-insulin-dependent diabetes mellitus (NIDDM) as of year 2012 (Data from 2014 National Diabetes Fact Sheet released by Centers for Disease Control and Prevention). The major defect in patients with type 2 diabetes is the functional impairment of insulin action on peripheral tissues to stimulate glucose uptake, to decrease gluconeogenesis, and to inhibit hepatic glucose output. Although these defects are caused by both genetic and environmental factors, the ultimate expression of diabetes is largely induced by environmental factors.<sup>1</sup> This fact implies that type 2 diabetes is preventable and curable. Understanding the molecular mechanisms of insulin resistance and glucose intolerance is very important in the treatment and prevention of diabetes. However, insulin-mediated signal transduction mechanisms are extremely complex, involving nearly 100 proteins and enzymes.<sup>2,3</sup> Thus, a complete understanding of these molecular mechanisms is unlikely in the near future. Insulin injection or oral intake of sulfonylurea derivatives (to stimulate pancreatic insulin secretion), and metformin (to inhibit hepatic glucose output), which can be toxic to humans,<sup>4</sup> are effective in lowering blood glucose levels but do not improve insulin resistance. Rosiglitazone and pioglitazone are thought to improve insulin resistance, but these agents pose potential risks for cardiac hypertrophy and liver damage.<sup>5,6</sup> Patients who utilize these conventional drugs in general do not attain normal glucose homeostasis nor do these drugs prevent diabetes.

Recently, the FDA approved glucagon-like protein-1 (GLP-1) for treating human diabetes. Although this agent helped to reduce HbA1c levels by 0.98% during a 16 weeks trial, there was a moderate to serious side effect of gastric discomfort.<sup>7</sup> Sixteen percent of subjects dropped out from the treatment group compared to 2% for the placebo group. Forty percent of subjects in the GLP-1 group experienced nausea, and 13% experienced vomiting. Since GLP-1 required continuous infusion or multiple subcutaneous injections to maintain its effectiveness due to rapid degradation by dipeptidyl peptidase-4 (DPP-4), GLP-1 was not expected to be feasible as a routine treatment for human diabetes.<sup>8</sup> More recently, the FDA approved a DPP-4 inhibitor for commercialization. In a 12 week, randomized, double-blind study in patients with type 2 diabetes the DPP-4 inhibitor at a daily dose of 100 mg decreased Hemoglobin (Hb) A1c by 0.39 to 0.56% ( $p < 0.05$ ) and fasting plasma glucose by 11.0 to 17.2 mg/dL ( $p < 0.05$ ) and was well-tolerated.<sup>9</sup> 100 mg DPP-4 inhibitor plus 2000 mg metformin treatment decreased HbA1c levels by 2.07% while metformin treatment alone reduced levels by 1.3 %. This meant that reduction of HbA1c by DPP-4 inhibitor was merely 0.77% above the level that was achieved by patients who continued on metformin alone.<sup>10</sup> Since there were no serious side effects with the DPP-4 inhibitor, this agent was considered a novel anti-diabetes agent for blood glucose control. However, DPP-4 inhibitors and GLP-1 do not improve insulin resistance.

The prevalence of overweight and obese subjects is increasing in the US with more than 70 % of the US population characterized as either overweight or obese and more than one third of the population either obese or extremely obese with BMI > 30.<sup>11</sup> More than 80 % of diabetic subjects are overweight or obese.<sup>12</sup> A body weight gain of 11 to 16 pounds more than doubled the incidence of type 2 diabetes compared to lean subjects while a gain of 17 to 24 pounds increased the risk three-fold.<sup>13</sup> Extensive counseling for diet and exercise improved weight loss in obese adults. At the same time, these subjects

had improved glucose metabolism, lipid levels, and blood pressure.<sup>14</sup> Thus, weight loss and blood sugar control are key components to the treatment of obesity-associated diabetes. Since Cyclo-Z treatment significantly improved insulin sensitivity in animal models of type 2 diabetes<sup>15,16</sup> and reduced body weight in obese rats,<sup>17</sup> we plan to investigate whether Cyclo-Z treatment improves both blood glucose and body weight in obese diabetic subjects in combination with control of diet and exercise.

## 1.2 Cyclo-Z (Cyclic dipeptide (his-pro) or CHP plus zinc)

Cyclo-Z is presented in a gel capsule form containing varying doses of CHP (3, 9 or 15 mg) and zinc (23 mg).

### Combination of CHP and zinc in the treatment of diabetes via stimulation of IDE synthesis:

Insulin degrading enzyme (IDE) is a zinc-containing enzyme that regulates degradation of internalized insulin and the maintenance of insulin sensitivity.<sup>18,19</sup> Diabetic animals and humans are zinc deficient<sup>20,21</sup> due to impaired intestinal zinc absorption and hyperzincuria.<sup>22,23,24,25,26</sup> Insulin bound to its receptor is transported to the endosome where it is separated from the insulin receptor. The inactive insulin is degraded to peptides and amino acids by IDEs. Under normal conditions, incompletely digested peptides in the endosome are completely digested in the lysosome. Incomplete digestion of the used insulin can interfere with the propagation of insulin-receptor-initiated signal transduction processes, thereby inducing insulin resistance (Fig. 1 below). If endosomal IDE levels are inadequate, undigested insulin will remain in the cytosol and prevent insulin signal transduction thereby disrupting the synthesis or translocation of glucose transporter-4 (GLUT-4) to the cell membrane for glucose uptake. Cyclo-Z enhances IDE synthesis and stimulates insulin degradation. Although Cyclo (his-pro) (CHP) or zinc alone are somewhat effective in the control of blood glucose metabolism, we hypothesize, based on the available literature and previous background studies, that the combination of CHP and zinc in Cyclo-Z work synergistically to ameliorate insulin resistance in diabetic and obese patients mainly by stimulating IDE synthesis.

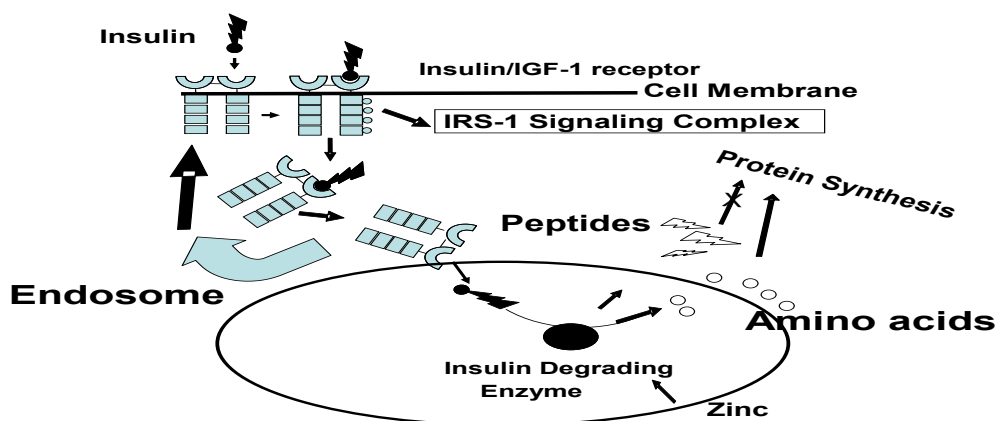


Figure 1: Degradation of Used Insulin in the Muscle and Fat Cells

### **1.3 Rationale for Study Population**

Cyclo-Z is a chemically pure agent whose uniform properties would make it more conducive to careful study. Thus, a formal Phase 1 clinical trial with Cyclo-Z was performed on 49 healthy volunteers. This double-blinded study showed no acute adverse side effects in subjects taking a one-time oral dose of 0, 2, 4, or 8 capsules of Cyclo-Z. All subjects had normal serum chemistry data and cell numbers at the start of the trial (0 hours) and no significant changes in these parameters from baseline occurred during 24 hours (0, 2, 4, 8, and 24 hours). Subjects (n = 12) who took 8 capsules of Cyclo-Z before breakfast showed significantly reduced blood glucose levels at 8 hours, but their plasma glucose levels remained within normal range. Twenty-four hours later, the blood glucose levels returned to baseline. In our animal studies, the optimal acute dose of Cyclo-Z was five times the daily dose required for long term diabetes treatment. Thus, this dose was only 70-80% of the acute optimal dose of Cyclo-Z shown to improve TAFGC values in diabetic animals. Since Cyclo-Z had mild glucose lowering effects in non-diabetic subjects who may or may not have had insulin resistance, we expect that this Phase 2 clinical trial with obese diabetic subjects will be successful in demonstrating blood sugar-lowering and/or weight loss with Cyclo-Z thereby providing “proof of concept” data.

## **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 Endpoints**

#### **3.1 Efficacy Evaluation**

The primary clinical efficacy variables used to evaluate the efficacy of Cyclo-Z are the change of HbA1c level from baseline at Week 12 and the change of body weight (BW) from baseline at Week 12.

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

#### **3.2 Exploratory Evaluation**

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 (TSH, T3, and T4)
- Serum Parameters: zinc, insulin, adiponectin, C-peptide, leptin, glucagon
- Urine Parameters: zinc, glucose, microalbumin, copper

#### **3.3 Safety Evaluation**

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

#### **3.4 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.



## **4. Investigational Plan**

### **4.1 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. Two or three clinical 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 (See Appendix 2).

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 Assessments and Section 6 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).

### **4.2 Selection of Study Population**

#### **4.2.1 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.

#### 4.2.2 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  $\geq 160$  mmHg or diastolic blood pressure  $\geq 95$  mmHg at Screening and Baseline.
  - Pulse rate  $\geq 95$  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  $\geq 1.5$  mg/dL for male or  $\geq 1.4$  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.

### **4.3 Subject Withdrawal**

Any subject is free to withdraw from participation in the study at any time, for any reason, specified or unspecified, and without prejudice to further treatment. The criteria for enrollment are to be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor/contract research organization (CRO) must be contacted. An exception may be granted in rare circumstances where there is a compelling reason to allow the subject to continue. In these rare cases, the investigator must obtain documented approval from the Sponsor or Sponsor designee to allow the subject to continue in the study.

In addition, subjects will be withdrawn from study drug and from the study in the following circumstances:

- The investigator decides that the subject should be withdrawn. If this decision is made because of an intolerable AE or a clinically significant laboratory value, if the dose of study drug has not been administered, it will be withheld and appropriate measures are to be taken. The Sponsor or Sponsor designee is to be notified immediately.
- The subject is unwilling to continue in the study.
- The subject is not compliant with the protocol.
- The investigator or the Sponsor, for any reason, stops the study.

If a subject prematurely withdraws from the study, every effort must be made to have the subject return to the clinical site for a premature termination visit. In all cases, the reason for withdrawal must be recorded in the Electronic Case Report Form (eCRF) and in the subject's medical records.

Contact will be maintained with subjects who are removed due to an AE until it has been resolved or stabilized, and the information will be documented in the eCRF and in the subject's medical records.

#### **4.4 Premature Termination of Study / Closure of Center**

The Sponsor has the right to terminate this study, and the investigator/Sponsor has the right to close a clinical site, at any time, although this should occur only after consultation between involved parties; the IRB must be informed in any case. Should the clinical site be closed prematurely, all study materials (e.g., study medication) must be returned to the Sponsor.

Discontinuation of the study may be necessary for medical or administrative reasons such as:

- Serious adverse events probably related to study drug administration so that the use of study drug may no longer be justifiable
- Significant change of benefit-risk ratio for the subjects
- The enrollment period has been exceeded
- The Sponsor discontinues the investigation of Cyclo-Z for type 2 diabetes indication or determines that the doses being studied are no longer justifiable

Possible reasons for closing of a clinical site include the following:

- The investigator feels that the number or severity of adverse events is excessive
- A change of technical, administrative, or personal circumstances occurs and the conduct of the study no longer meets ICH-GCP guidelines
- In case of evident, significant non-compliance to protocol or poor data quality
- The enrollment rate at a clinical site is unlikely to result in the recruitment of the required subject numbers.

## 5. Study Treatments

### 5.1 Treatment to be Administered

At Visits 2, 3, 4, 5, 6, and 7 (Weeks 0, 2, 4, 6, 8, and 10), each subjects will be dispensed with study drug supply for a 2-week period (14 capsules plus 4 extra capsules, total 18 capsules). The subjects will be instructed to orally administer one capsule just before bedtime each day.

All subjects will be instructed to continue their current diabetes medications and all other prescribed drugs.

### 5.2 Identity of Investigational Product

Investigational products are white-color capsules and supplied to clinical sites in HDPE bottles. Placebo capsules will be matched for Cyclo-Z capsules in color, shape, and size and will be indistinguishable from Cyclo-Z capsules. All manufacturing and packaging activities will be performed according to cGMP guidelines.

Each bottle has a label including the following information:

- Product name
- Randomization number
- Dosage form information
- Protocol number
- Lot number
- Dosing instruction
- Storage condition
- Cautionary statement
- Sponsor name and contact information

All drug supplies must be stored in a secure area (e.g., locked cabinet), at controlled room temperature 15~30 °C (59~86 °F).

### 5.3 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 the Sponsor. 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

#### **5.4 Selection of Doses in the Study**

The doses of Cyclo-Z were chosen on the basis of results of non-clinical efficacy and safety studies. The detailed results are documented in the Investigator's Brochure.

#### **5.5 Choice of Controls/Comparators**

This study uses an inert placebo as a negative control. The purpose of this is to reduce all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic or toxicological action of the study medication.

#### **5.6 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.

#### **5.7 Prior and Concomitant Treatments**

All the subjects will be instructed to continue their current diabetes medications and all other prescribed drugs. All prior (2 months prior to Screening) and concomitant medications must be entered into the electronic case report form (eCRF), including the name of the drug or treatment, dose, route of administration, date and time of the treatment, and indication. In the event that prior or concomitant medication is administered, the investigator must access the subject's eligibility of continuing the participation in the study.

The following medications are not allowed to be taken by subjects enrolled in this study during the trial:

- Psychoactive agents such as monoamine oxidase inhibitors and antidepressive agents (e.g., lithium, Prozac, Zoloft, Serzone, Paxil, Effexor)
- Any other medications that may pose harm to the subject

- Any investigational drug (including placebo)

## **5.8 Subject Education on Hypoglycemia/Hyperglycemia and its Management**

All subjects will be instructed in life style modification and asked to maintain a stable diet and daily exercise routine and to keep a daily record of their blood glucose level before breakfast and 2 hours after dinner. Hypo- or hyperglycemia are of particular concern and if either occurs, it will be handled in a standard fashion as outlined in Section 9.5, Procedures for Managing Hypoglycemia and Hyperglycemia.

Although Cyclo-Z treatment alone does not cause hypoglycemia in human as demonstrated in the prior informal study, it may potentially lead to hypoglycemia when interacting with other anti-diabetic drugs. The interaction between Cyclo-Z and other oral anti-diabetic agents or obesity medications are not known at this time. However, some anti-diabetic agents such as insulin injection, sulfonyl derivatives or other insulin secretion stimulating agents may cause hypoglycemia regardless of Cyclo-Z treatment. Improved insulin resistance during the study requires reduction in the use of other insulin and insulin secretagogues. Thus, subjects' blood glucose levels should be closely monitored to detect hypoglycemia in order for the use of other anti-diabetic agents to be appropriately reduced. For the purpose of record keeping and maintaining subject's health, all subjects will be provided with their own glucometer to measure their blood glucose levels. If there are subjects with a possibility of developing acute hypoglycemia while using their current hypoglycemic agents concomitantly with Cyclo-Z, they will be instructed to carry commercial glucose tablets with them to take when feeling dizzy and weak. While taking Cyclo-Z, an improvement in insulin sensitivity or symptoms of hypoglycemia will not develop acutely. Furthermore, 2-week periodical examinations and subjects' daily blood glucose measurements will keep their glucose levels on track and help prevent them from experiencing possible hypoglycemic episodes.

At the same time, hyperglycemia will be well maintained by examining subjects bi-weekly. Taking Cyclo-Z may increase fasting blood glucose initially for 2 months due to the reduction in pancreatic insulin secretion, which could occur with improved insulin sensitivity. Subjects will be instructed to monitor for increased thirst, urination and blurry vision, but subjects will also be advised that the best method for detecting hyperglycemia is by measuring blood glucose level.

## **5.9 Medication Accountability and Treatment Compliance**

Subjects will return all unused study medications with the diary at Visits 3, 4, 5, 6, 7, and 8 (Weeks 2, 4, 6, 8, 10, and 12) or at Early Termination Visit. The returned medications and diaries will be reviewed with the subject to evaluate the medication accountability and treatment compliance. If a subject misses 3 or more doses out of total 2-week doses (i.e., 14 doses), the site should contact the Sponsor for the discussion of potential early termination.

All study medication supplies should be accounted for at the termination of the study and a written explanation provided for discrepancies. All unused study medication supplies and packaging materials are

to be inventoried and returned to the Sponsor by the investigator. The investigator is not permitted to return or destroy unused clinical drug supplies or packaging materials unless authorized by the Sponsor.

The medication doses for the diabetes treatment should not be changed during the 3-month treatment period.



## 6. Study Procedures

Refer to the Schedule of Assessments for an outline of study specific procedures/assessments required at each visit. Additional procedures as part of standard of care may be performed whenever the investigator determines it is necessary.

The study duration for each subject may be up to 16 weeks. This includes a 2-week screening period, a 12-week treatment period from randomization to the last treatment visit, and a 2-week safety follow up period. All visits from Visit 2 should occur within 6 days (i.e.,  $\pm 3$  days) from the initial schedule for Visits 3 to 8 and within 7 days (i.e., + 7 days) for Visit 9, respectively.

Each subject will be required to visit the clinical site, in a fasted state, before breakfast approximately 9 times over a period of 16 weeks starting at Screening. All missed visits and any procedures that are not performed per protocol must be documented in the source documents and the appropriate CRF.

### 6.1 Screening Period

A screening visit will occur at least 2 weeks prior to the randomization.

A signed and dated Institutional Review Board (IRB) approved Informed Consent Form must be obtained before any study-specific procedures are performed. Once written informed consent has been obtained, the following screening procedures and assessments must be performed to determine eligibility and document adherence to the preliminary inclusion/exclusion criteria:

- Record demographic data (i.e., date of birth, race, and height).
- Record relevant medical history including diabetic history.
- Record details of previous medications.
- Perform a physical examination.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Measure 12-lead ECG.
- Collect blood samples for hematology, serum chemistry, HbA1c, and pregnancy test (serum hCG).
- Dispense daily log with blood glucose monitoring devices to record daily blood glucose values (fasting before breakfast and two hours after dinner) and study medication adherence (See Appendix 2).

### 6.2 Treatment Period

#### 6.2.1 Visit 2 (Week 0): Baseline

Visit 2 will occur after the completion of 2-week assessment (+7 days). During this visit, the following procedures and assessments must be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a physical examination.

- Collect daily logs and blood glucose monitoring devices and review daily logs with the subject.
- Record any changes in concomitant medications.
- Record an adverse event, if applicable.
- Assess hypoglycemic and hyperglycemic episodes (See Appendix 4).
- Confirm the inclusion and exclusion criteria.
- Randomize the subject
- Conduct the ADDQoL Questionnaire (See Appendix 3).
- Perform the OGTT (See Appendix 1)
- Measure waist circumference.
- Collect blood samples for hematology, serum chemistry, HbA1c, FPG, and thyroid function test (TSH, T3, and T4).
- Collect blood samples\* for zinc, insulin, adiponectin, C-peptide, leptin, and glucagon.
- Collect urine samples for glucose, microalbumin, copper, and zinc.
- Dispense study medications to the subject with detailed instructions.
- Dispense daily log with blood glucose monitoring devices to record daily blood glucose values (fasting before breakfast and two hours after dinner) and study medication adherence (See Appendix 2).

\*If residual plasma and/or serum are available, CHP levels may be measured.

#### 6.2.2 Visits 3, 5, and 7 (Weeks 2, 6, and 10)

Each study visit will occur 2 weeks ( $\pm$  3 days) after the previous visit. During each visit, the following procedures and assessments must be performed:

- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Review adverse events and concomitant medications.
- Assess hypoglycemic and hyperglycemic episodes (See Appendix 4).
- Collect daily logs and blood glucose monitoring devices and review daily logs with the subject.
- Collect unused study medications and review the medication accountability with the subject.
- Dispense study medications to the subject.
- Dispense daily log with blood glucose monitoring devices to record daily blood glucose values (fasting before breakfast and two hours after dinner) and study medication adherence (See Appendix 2).

#### 6.2.3 Visits 4 and 6 (Weeks 4 and 8)

Each study visit will occur 2 weeks ( $\pm$  3 days) after the previous visit. During each visit, the following procedures and assessments must be performed:

- Collect daily logs and blood glucose monitoring devices and review daily logs with the subject.
- Collect unused study medications and review the medication accountability with the subject.
- Review adverse events and concomitant medications.
- Assess hypoglycemic and hyperglycemic episodes (See Appendix 4).
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.

- Perform a physical examination.
- Measure waist circumference.
- Collect blood samples for hematology, serum chemistry, HbA1c, and FPG.
- Collect blood samples\* for zinc, insulin, adiponectin, C-peptide, leptin, and glucagon.
- Collect urine samples for glucose, microalbumin, copper, and zinc.
- Dispense study medications to the subject.
- Dispense daily log with blood glucose monitoring devices to record daily blood glucose values (fasting before breakfast and two hours after dinner) and study medication adherence (See Appendix 2).

\*If residual plasma and/or serum are available, CHP levels may be measured.

#### 6.2.4 Visit 8 (Week 12) or Early Termination Visit

This study visit will occur 2 weeks ( $\pm$  3 days) after Visit 7 or when the subject is early terminated due to any reason. During this visit, the following procedures and assessments must be performed:

- Conduct the ADDQoL Questionnaire (See Appendix 3).
- Collect daily logs and blood glucose monitoring devices and review daily logs with the subject.
- Collect unused study medications and review the medication accountability with the subject.
- Perform the OGTT (See Appendix 1)
- Assess hypoglycemic and hyperglycemic episodes (See Appendix 4).
- Review adverse events and concomitant medications.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.
- Perform a physical examination.
- Measure waist circumference.
- Measure 12-lead ECG.
- Collect blood samples for hematology, serum chemistry, HbA1c, FPG, thyroid function test (TSH, T3, and T4), and pregnancy test (serum hCG).
- Collect blood samples\* for zinc, insulin, adiponectin, C-peptide, leptin, and glucagon.
- Collect urine samples for glucose, microalbumin, copper, and zinc.

\*If residual plasma and/or serum are available, CHP levels may be measured.

### 6.3 Follow-up Period

The safety follow-up visit will occur at least 2 weeks after the last dose (+ 7 days). During this visit, the following procedures and assessments must be performed:

- Review adverse events and concomitant medications.
- Measure vital signs (sitting blood pressure, pulse, breathing, and temperature) and weight.

#### **6.4 Other Information for Study Visits**

Unscheduled visits and/or procedures may be required in addition to the visits and procedures detailed above. The additional visits or procedures are at the discretion of the investigator. The details of these unscheduled visits or procedures will be recorded in the source documents and entered into the eCRFs.

If a subject misses a scheduled visit, the clinical site is to make every effort to have the subject visit the site as soon as possible. If a subject may delay 7 or more days from the scheduled date, the site should contact the Sponsor for the discussion of how to determine.

#### **6.5 Data Quality**

Monitoring and auditing procedures defined/agreed by the Sponsor will be followed in compliance with current GCP guidelines. Each clinical site will be visited at regular intervals (about 6 weeks) by a monitor to ensure compliance with the study protocol, GCP guideline, and other regulatory aspects. This will include on-site review of the source documents and eCRFs for the completeness and clarity, consistency between source documents and eCRFs, and clarification of administrative matters.

#### **6.6 Documentation**

Entries made in the eCRF must be either verifiable against source documents or have been directly entered into the eCRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained/archived until notification by the Sponsor for change of archive site or destruction.

## **7. Ethical and Legal Aspects**

### **7.1 Institutional Review Board (IRB)**

Documented approval from the IRB will be obtained for all participating clinical site(s) prior to study start, according to GCP and applicable laws and regulations. When necessary, an extension, amendment, or renewal of the IRB approval must be obtained and also forwarded to the Sponsor. The IRB must supply to the Sponsor, upon request, a list of the IRB members involved in the vote and a statement to confirm that the IRB is organized and operates according to GCP and applicable laws and regulations.

### **7.2 Ethical Conduct of the Study**

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the Sponsor representatives and/or Regulatory Authority representatives at any time. The investigator must agree to the inspection of study-related records by the Regulatory Authority/Sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/Sponsor representatives.

Modifications to the study protocol will be implemented by the investigator only after the Sponsor's approval. However, the investigator may implement a deviation form, or change of the protocol to eliminate any immediate hazard(s) to the trial subjects without prior IRB/Sponsor approval. The implemented deviation or change, the reasons for it and, if appropriate, the proposed amendment should be submitted to the IRB/Sponsor as soon as possible. Any deviations from the protocol must be fully explained and documented by the investigator.

### **7.3 Regulatory Authority Approvals/Authorizations**

Regulatory Authority approvals/authorizations/notifications, where required, will be in place and fully documented prior to the study's start.

### **7.4 Subject Information Consent**

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the IRB written approval of the Informed Consent Form and any other written information that will be provided to the subjects. The written approval of the IRB with the approved Informed Consent Form must be in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject's files.

### **7.5 Insurance**

All subjects participating in the study will have insurance coverage by the Sponsor, which is in line with applicable laws and/or regulations.

### **7.6 Confidentiality**

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number and subject initials will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Even if the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified.

## **8. Statistical Methods and Determination of Sample Size**

### **8.1 Statistical and Analytical Plan**

#### 8.1.1 Analytical Populations

##### Intent-to-Treat Population

An intent-to-treat (ITT) population will include subjects who have administered at least one dose of study medication and who have baseline and any post-baseline efficacy data. This cohort will be evaluated for all efficacy variables.

##### Per-Protocol Population

All subjects valid for ITT 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.

Additional criteria may be added prior to unblinding the study database.

As with the ITT population, this per-protocol (PP) cohort will also be evaluated for all efficacy variables.

##### Safety Population

Any subject who administers at least one dose of study medication and has any post-randomization safety data collected will be included in the evaluation of safety.

#### 8.1.2 Treatment Group Comparability

Demographic variables, medical history, treatment duration, and efficacy variables at baseline will be summarized by treatment group for the subjects valid for potential safety analysis. Because, in theory, the goal of randomization is to balance out the patient characteristics, statistical tests are not planned for these variables.

#### 8.1.3 Primary Efficacy Analyses

The change from baseline to Week 12 in HbA1c will be compared for the experimental groups versus the control group using analysis of variance (ANOVA) methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used. 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.

The change from baseline to Week 12 in BW will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

#### 8.1.4 Secondary Efficacy Analyses

The change from baseline to Week 12 in FPG level will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

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 testing methods or Fisher's exact tests, as appropriate.

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 testing methods or Fisher's exact tests, as appropriate.

The change from baseline to Week 12 in waist circumference will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

The change from baseline to Week 12 in mean value of postprandial (2 hours after dinner) blood glucose level for 2 weeks will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

The change from baseline to Week 12 in OGTT will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

The change from baseline to Week 12 in ADDQoL questionnaire scores will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.

#### 8.1.5 Exploratory Efficacy Analyses

The change from baseline to Week 12 in thyroid function test (TSH, T3, T4), serum parameters (insulin, adiponectin, C-peptide, leptin, glucagon), and urine parameters (zinc, glucose, microalbumin, copper) will be compared for the experimental groups versus the control group using ANOVA methods if the change is approximately normally distributed. If the change is markedly non-normally distributed then Wilcoxon rank sum tests will be used.



### 8.1.6 Safety Analyses

Safety variables will be summarized with descriptive statistics, overall and by each of the four groups, separately. The safety variables include: Blood samples, ECG evaluation, physical examination endpoints, vital signs, adverse events (AEs) and episodes of hypoglycemia and hyperglycemia. Continuous safety variables will be summarized with means, standard deviations, medians and ranges. Categorical safety variables will be summarized with counts and percentages.

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities). AEs will be summarized by System Organ Class (SOC) and Preferred Term (PT). AEs will also be summarized by relationship to the study drug, seriousness and severity.

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.

Statistical tests are not planned for safety variables.

### 8.1.7 CHP Concentration Analyses

Levels of CHP may be assessed in blood for a subset of subjects if there are residual serum and/or plasma after completion of protocol-required tests. No statistical tests are planned for these data.

### 8.1.8 Missing Data

No adjustments for missing data and no imputation methods are planned for this phase 2 study.

### 8.1.9 General Statistical Considerations

Continuous variables will be summarized with means, standard deviations, medians and ranges. Categorical variables will be summarized with counts and percentages. P-values less than or equal to 0.05 will be considered statistically significant. Because this is a phase 2 clinical trial and because it was not formally powered with statistical algorithms, no adjustments for multiple comparisons will be made to the results presented in this study.

## 8.2 Determination of Sample Size

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.

### **8.3 Interim Analyses**

No interim analyses are planned for this Phase 2 study.

## **9. ADVERSE EVENTS**

### **9.1 Warnings / Precautions**

This study medication must be kept out of reach of children. See the Investigator's Brochure for additional information.

### **9.2 Adverse Event Monitoring**

Subjects must be carefully monitored for AEs. AEs should be assessed in terms of their seriousness, severity, and relationship to the study drug.

### **9.3 Adverse Event Definitions**

#### **9.3.1 Adverse Event (AE)**

An AE is any untoward medical occurrence in a clinical trial subject administered with an investigational product under investigation. The AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

AEs associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An AE occurring in the course of the use of a drug product in professional practice;
- An AE occurring from an overdose whether accidental or intentional;
- An AE occurring from drug abuse;
- An AE occurring from drug withdrawal;
- An AE where there is a reasonable possibility that the event occurred purely as a result of the subject participation in the study (e.g. AE or SAE due to discontinuation of ant-depressants during wash-out phase) must also be reported as an AE, even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE, if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for a 'serious' AE, it must be recorded and reported as such.

#### **9.3.2 Serious Adverse Event (SAE)**

An SAE is any untoward medical occurrence that at any dose:

- Results in death;
- 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.

**Life-threatening:** The term ‘life-threatening’ in the definition of ‘serious’ refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE that hypothetically might have caused death if it were more severe.

**Hospitalization:** Any AE leading to hospitalization or prolongation of hospitalization will be considered as ‘serious’, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours OR,
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) OR,
- The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a SAE dependent on clinical judgment.

**Disability** means a substantial disruption of a person’s ability to conduct normal life’s functions.

**Important medical event:** Any AE may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the ‘WHO Adverse Reaction Terminology – Critical Terms List’. These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

### 9.3.3 Unexpected Adverse Event

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the info presented in the current Investigator’s Brochure. Also, reports that add significant information on specificity or severity of known, already documented AE constitute unexpected AEs. For example, an AE more specific or more severe than described in the Investigator’s Brochure would be considered ‘unexpected’. Specific examples would be: (a) acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

### 9.3.4 Relationship of Adverse Event to Investigational Product

The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF.

An assessment of 'No' would include:

- The existence of a clear alternative explanation (e.g., mechanical bleeding at surgical site);
- Non-Plausibility (e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event);
- Cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the AE is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the AE to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subject's response after drug reintroduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drug the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the test drug, coupled with the individual subject's pharmacodynamics should be considered.

### 9.3.5 Severity of Adverse Event

The severity of AEs should be graded as follows:

Mild – Usually transient in nature and generally not interfering with normal activities

Moderate – Sufficiently discomforting to interfere with normal activities

Severe – Prevents normal activities

### 9.3.6 Adverse Event Documentation

All AEs occurring after the subject has signed the informed consent must be fully recorded in the subject's CRF.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken, and outcome.

#### **9.4 Reporting of Serious Adverse Events/Pregnancy**

SAEs, including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent, and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person/parties as detailed in the study file. A SAE form must also be completed within 24 hours of the investigator's awareness and forwarded to the designated person/parties as detailed in the study file. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated person/parties.

When required, and according to local law and regulations, SAEs must be reported to the IRB and Regulatory Authorities.

Pregnancy occurring during a clinical investigation, although not considered a SAE, must be reported to the Sponsor within the same timelines as a SAE on Pregnancy Monitoring Form. The outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

#### **9.5 Procedures for Managing Hypoglycemia and Hyperglycemia**

Subjects will continue to be on their usual diabetes medications including insulin, sulfonylurea, metformin and/or glitathiazone derivatives. If a subject develops hypoglycemia during the study period per definitions stated in Appendix 4, the doses of antidiabetic agents will be adjusted to maintain glycemic control levels (fasting plasma glucose between 70-130 mg/dl). The standard of care mandated by the American Diabetes Association and optimal healthcare for all participants while meeting the study needs will be followed by the Investigator. Specifically, subjects will monitor and record their daily glucose levels twice daily (before breakfast and 2 hours after dinner) and be seen by the Investigator at each visit.

If during this time a subject experiences hypoglycemia more than twice, he/she must consult with the Investigator. Reasons for hypoglycemia will be sought such as changes in dietary or exercise patterns. If there is no apparent reason for hypoglycemia, then a subject on insulin will be instructed to reduce his/her insulin dose by 4 units or 10% of his/her usual insulin dose, observe the effects of the dose reduction for 3 days, and then report to the Investigator. If the subject continues to develop hypoglycemia, the dose of insulin will be reduced by another 2-4 units. Similarly, if the subject is on an oral hypoglycemic agent they will be instructed to reduce the dose of their oral hypoglycemic agent in a stepwise fashion. This life style modification is mandatory in the study protocol although the Investigator cannot monitor the individual's compliance to the instruction. Subjects who experience symptomatic hypoglycemia will be instructed to ingest a rapidly absorbed sugar. The most convenient fast-acting sugar is found in glucose tablets or gels and will be provided to subjects. These interventions will be subject-specific and must be undertaken under the direction of the Investigator and/or their own health provider to prevent and solve unforeseen hypoglycemic problems.

If a subject experiences serious hypoglycemia on a frequent basis, the Investigator may direct the subject to discontinue the use of all anti-diabetic drug intake and insulin injections and may also discontinue the use of the study drug until the cause of the hypoglycemia is determined. The subject will be instructed to continue to follow the protocol for record keeping, blood analysis and others.

If a subject experiences an increase in FPG level of >270 mg/dl from baseline to Week 6 or >240 mg/dl from Week 6 to 12, the subject will be instructed to take his/her own hypoglycemic agent. It is expected that glucose levels can be controlled in most diabetic subjects by these treatments. If the subject's blood glucose levels do not decrease to an acceptable level (<240 mg/dl) after 2 weeks, the subject will be referred to a diabetologist and will be terminated from the study. The study physician will continue to evaluate and treat the subject as needed until healthcare is turned over to the diabetologist.

## **10. USE OF DATA AND PUBLICATION**

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor, who may utilize the data in various ways, such as for submission to government regulatory authorities or disclosure to other investigators. The investigator, while free to utilize data derived from the study for scientific purposes, must discuss any publication with the Sponsor prior to release and obtain written consent of the Sponsor on the intended publication. The Sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to the Sponsor thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between the Sponsor and the investigator(s), the contents of the publication will be discussed in order to find a solution that satisfies both parties.

The investigator is encouraged to participate in the evaluation of the data for scientific purposes but is expected to work with the Sponsor in the development of any scientific presentation or publication. Since the Sponsor authors will be included, it is expected that all co-authors of the manuscripts will have an opportunity for feedback in the content and conclusions. The technical and editorial resources of the Sponsor will be available to assist in the development of abstracts, presentations, and publications regarding this study, and it is expected that drafts will be sent to the Sponsor with adequate time for input and revisions prior to submission.



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## **12. APPENDICES**

### **Appendix 1: Oral Glucose Tolerance Test (OGTT)**

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.

**Appendix 2: Daily Log**

**Subject Diary**

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

<b>Protocol No.</b>	<b>NMP-CYZ-P2-001</b>						
<b>Subject Initial</b>	<table border="1" style="width: 100%; height: 30px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>						
<b>Screening No.</b>	<table border="1" style="width: 100%; height: 30px;"> <tr> <td style="width: 25%;"></td> <td style="width: 25%; text-align: center;">-</td> <td style="width: 25%;"></td> <td style="width: 25%;"></td> </tr> </table>				-		
	-						
	Code*		Number				

\* Site Number

**< How to fill out this diary >**

- Please record this diary everyday starting the evening of the day it's dispensed until the morning of your next visit to the hospital.
- Return this diary to the person in charge of this study at your next visit. You will receive a new diary at each visit.
- Study Site: This is the name of the hospital you will be visiting for the study.
- Date Dispensed: This is the date you received this diary. Please record it in the format of DD/MMM/YYYY (Example: 03 Feb 2015).
- Date: This is the date you checked your blood sugar levels and took the study medication. Please record it in the format of DD/MMM/YYYY (Example: 03 Feb 2015).
- Blood Sugar: Please check the unit in which your blood sugar level is measured.
- Fasting before breakfast: Write down your blood sugar level tested in a fasted state before breakfast.
- 2 hours after dinner: Write down your blood sugar level tested 2 hours after dinner.
- Not done: If you did not check your blood sugar, please check the box and state the reason.
- Study Medication: Please check whether you took the study medication or not. On the evening before your visit to the hospital, indicate when you took study medication in a 24 hour format (Example: 6:00 pm = 18:00, 8:00 pm = 20:00).
- Not taken: If you did not take your study medication, please check the box and state the reason.
- If you are unable to return to the study site 14 days after your previous visit, use the additional rows provided to continue recording your blood sugar levels and the study medication compliance until your next visit.
- Comments: Please leave any comments, questions or concerns you may have. Also inform the study staff of any changes to your diet or exercise regimen.
- Diary return date and confirmation signature: Please record the date the diary is returned to the site and your signature to confirm.

*If you have any further questions or problems about filling out the diary or the study in general, please contact your clinical site.*

Date Dispensed		(Example: 03 Feb 2015)	
Day	Date (DD/MMM/YYYY)	Blood Sugar ( <input type="checkbox"/> mg/dl <input type="checkbox"/> mmol/L)	
1		Fasting before breakfast	2 hours after dinner
		N/A	
		<input type="checkbox"/> Not done (reason: )	
Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )			
2		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
3		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
4		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
5		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
6		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
7		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
8		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
9		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
10		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	
11		Fasting before breakfast	2 hours after dinner
		<input type="checkbox"/> Not done (reason: )	
		Study Medication: <input type="checkbox"/> Taken <input type="checkbox"/> Not taken (reason: )	

12		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
13		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
14		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
()		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
()		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
()		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
()		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
()		Fasting before breakfast	2 hours after dinner
		□Not done (reason: )	
		Study Medication: □Taken □Not taken (reason: )	
Time you took your medication the evening before your visit to hospital:			
<b>Comments</b>			
Please leave any comments, questions or concerns you may have. Also inform the study staff of any changes to your diet or exercise regimen.			

Please fill out the following when you return the diary at each visit.

<b>Diary Return Date (DD/MMM/YYYY)</b>	
<b>Subject Signature</b>	
<b>Reviewer Signature</b>	

### Appendix 3: Audit of Diabetes-Dependent Quality of Life (ADDQoL) Questionnaire

## ADDQoL

This questionnaire asks about your quality of life – in other words how good or bad you feel your life is.

Please put an "X" in the box that best indicates your response for each item.

What we want to know is how you feel about your life now.

I) In general, my present quality of life is:						
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
excellent	very good	good	neither good nor bad	bad	very bad	extremely bad

Now we would like to know how your quality of life is affected by your diabetes, its management and any complications you may have.

II) If I did <u>not</u> have diabetes, my quality of life would be:				
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
very much better	much better	a little better	the same	worse

Please respond to the more specific items on the pages that follow. For each aspect of life described, you will find two parts:

For Part (a): put an "X" in one box to show how diabetes affects this aspect of your life;  
For Part (b): put an "X" in one box to show how important this aspect of your life is to your quality of life.

<b>1</b>	<b>(a)</b>	<b>If I did <i>not</i> have diabetes, I would enjoy my leisure activities:</b> <input type="checkbox"/> very much more <input type="checkbox"/> much more <input type="checkbox"/> a little more <input type="checkbox"/> the same <input type="checkbox"/> less
	<b>(b)</b>	<b>My leisure activities are:</b> <input type="checkbox"/> very important <input type="checkbox"/> important <input type="checkbox"/> somewhat important <input type="checkbox"/> not at all important

<b>2</b>	<b>Are you currently working, looking for work or would like to work?</b> Yes <input type="checkbox"/> If yes, complete (a) and (b). No <input type="checkbox"/> If no, go straight to Question 3.
	<b>(a) If I did <i>not</i> have diabetes, my work life would be:</b> <input type="checkbox"/> very much better <input type="checkbox"/> much better <input type="checkbox"/> a little better <input type="checkbox"/> the same <input type="checkbox"/> worse
	<b>(b) For me, having a work life is:</b> <input type="checkbox"/> very important <input type="checkbox"/> important <input type="checkbox"/> somewhat important <input type="checkbox"/> not at all important

<b>3</b>	<b>(a)</b>	<b>If I did <i>not</i> have diabetes, local or long distance travel would be:</b> <input type="checkbox"/> very much easier <input type="checkbox"/> much easier <input type="checkbox"/> a little easier <input type="checkbox"/> the same <input type="checkbox"/> more difficult
	<b>(b)</b>	<b>For me, local or long distance travel are:</b> <input type="checkbox"/> very important <input type="checkbox"/> important <input type="checkbox"/> somewhat important <input type="checkbox"/> not at all important



<b>4</b>	<p><b>Do you ever go on vacation or want to go on vacation?</b>                  Yes <input type="checkbox"/> If yes, complete (a) and (b).                  No <input type="checkbox"/> If no, go straight to Question 5.</p>
<b>(a)</b>	<p><b>If I did <u>not</u> have diabetes, my vacations would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very much better    much better    a little better    the same    worse             </p>
<b>(b)</b>	<p><b>For me, vacations are:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very important    important    somewhat important    not at all important             </p>

<b>5 (a)</b>	<p><b>If I did <u>not</u> have diabetes, physically I could do:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very much more    much more    a little more    the same    less             </p>
<b>(b)</b>	<p><b>For me, how much I can do physically is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very important    important    somewhat important    not at all important             </p>

<b>6</b>	<p><b>Do you have any family/relatives?</b>                  Yes <input type="checkbox"/> If yes, complete (a) and (b).                  No <input type="checkbox"/> If no, go straight to Question 7.</p>
<b>(a)</b>	<p><b>If I did <u>not</u> have diabetes, my family life would be</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very much better    much better    a little better    the same    worse             </p>
<b>(b)</b>	<p><b>My family life is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very important    important    somewhat important    not at all important             </p>

<b>7 (a)</b>	<p><b>If I did <u>not</u> have diabetes, my friendships and social life would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very much better    much better    a little better    the same    worse             </p>
<b>(b)</b>	<p><b>My friendships and social life are:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                  very important    important    somewhat important    not at all important             </p>

<b>8</b>	<p><b>Do you have or would you like to have a close personal relationship (e.g. husband / wife, partner)?</b></p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to Question 9.</p>
<b>(a)</b>	<p><b>If I did <u>not</u> have diabetes, my closest personal relationship would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very much better      much better      a little better      the same      worse             </p>
<b>(b)</b>	<p><b>For me, having a close personal relationship is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very important      important      somewhat important      not at all important             </p>

<b>9</b>	<p><b>Do you have or would you like to have a sex life?</b></p> <p>Yes <input type="checkbox"/> If yes, complete (a) and (b).</p> <p>No <input type="checkbox"/> If no, go straight to Question 10.</p>
<b>(a)</b>	<p><b>If I did <u>not</u> have diabetes, my sex life would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very much better      much better      a little better      the same      worse             </p>
<b>(b)</b>	<p><b>For me, having a sex life is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very important      important      somewhat important      not at all important             </p>

<b>10 (a)</b>	<p><b>If I did <u>not</u> have diabetes, my physical appearance would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very much better      much better      a little better      the same      worse             </p>
<b>(b)</b>	<p><b>My physical appearance is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very important      important      somewhat important      not at all important             </p>

<b>11 (a)</b>	<p><b>If I did <u>not</u> have diabetes, my self-confidence would be:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very much better      much better      a little better      the same      worse             </p>
<b>(b)</b>	<p><b>My self-confidence is:</b></p> <p style="text-align: center;"> <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/>                      <input type="checkbox"/> </p> <p style="text-align: center;">                 very important      important      somewhat important      not at all important             </p>

<b>12 (a)</b>	<b>If I did <u>not</u> have diabetes, my motivation would be:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		very much better	much better	a little better	the same	worse
<b>(b)</b>	<b>My motivation is:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		very important	important	somewhat important	not at all important	

<b>13 (a)</b>	<b>If I did <u>not</u> have diabetes, the way people in general react to me would be:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		very much better	much better	a little better	the same	worse
<b>(b)</b>	<b>The way people in general react to me is:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		very important	important	somewhat important	not at all important	

<b>14 (a)</b>	<b>If I did <u>not</u> have diabetes, my feelings about the future (e.g. worries, hopes) would be:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		very much better	much better	a little better	the same	worse
<b>(b)</b>	<b>My feelings about the future are:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		very important	important	somewhat important	not at all important	

<b>15 (a)</b>	<b>If I did <u>not</u> have diabetes, my financial situation would be:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		very much better	much better	a little better	the same	worse
<b>(b)</b>	<b>My financial situation is:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		very important	important	somewhat important	not at all important	

<b>16 (a)</b>	<b>If I did <u>not</u> have diabetes, my living situation and conditions would be:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		very much better	much better	a little better	the same	worse
<b>(b)</b>	<b>My living situation and conditions are:</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
		very important	important	somewhat important	not at all important	

<b>17 (a)</b>	<b>If I did <u>not</u> have diabetes, I would have to depend on others when I do not want to:</b>			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
very much less	much less	a little less	the same	more
<b>(b)</b>	<b>For me, not having to depend on others is:</b>			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
very important	important	somewhat important	not at all important	

<b>18 (a)</b>	<b>If I did <u>not</u> have diabetes, my freedom to eat as I want would be:</b>			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
very much greater	much greater	a little greater	the same	less
<b>(b)</b>	<b>My freedom to eat as I want is:</b>			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
very important	important	somewhat important	not at all important	

<b>19 (a)</b>	<b>If I did <u>not</u> have diabetes, my freedom to drink as I want (e.g. fruit juice, alcohol, sweetened hot and cold drinks) would be:</b>			
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
very much greater	much greater	a little greater	the same	less
<b>(b)</b>	<b>My freedom to drink as I want is:</b>			
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
very important	important	somewhat important	not at all important	

Are there any other ways in which diabetes, its management and any complications affect your quality of life? If so, please write what they are below.

For information only
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Thank you for completing this questionnaire.

#### **Appendix 4: Determining Hypoglycemic and Hyperglycemic Episodes**

For this study, a subject will be described as having hypoglycemic or hyperglycemic episodes when the following definitions are met:

- Documented Symptomatic Hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration  $\leq 70$  mg/dl.
- Asymptomatic Hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration  $\leq 70$  mg/dl.
- Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but that was presumably caused by a plasma glucose concentration  $\leq 70$  mg/dl.
- Relative Hypoglycemia is defined as an event during which the person with diabetes reports of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration  $> 70$  mg/dl.
- Severe Hypoglycemia is defined as an event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions, or when a measured plasma glucose concentration is  $< 40$  mg/dl.
- Hyperglycemia is defined as plasma glucose level  $> 140$  mg/dl.
- Severe hyperglycemia is defined as plasma glucose level  $> 300$  mg/dl.

\* *Definitions of hypoglycemic episodes were defined per "Defining and Reporting Hypoglycemia: A report from the American Diabetes Association Workgroup on Hypoglycemia" from May, 2005 issue of Diabetes Care.*