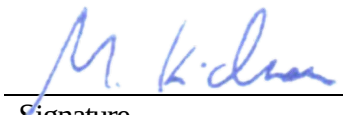
Clinical Study Protocol: ORA-D-013-3

Study Title:	A Double-Blinded, Placebo-controlled, Double Dummy, Multi-center Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in Subjects with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on One to Three Glucose-lowering Agents
Protocol Number:	ORA-D-013-3
Study Phase:	Phase 3
Sponsor:	Oramed Ltd. 20 Mamilla Avenue Jerusalem, 9414904, Israel
Name of Sponsor Signatory:	Miriam Kidron, PhD Chief Scientific Officer and Director Oramed Ltd.
Protocol Version:	4
Date of Version:	November 10, 2024

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned has reviewed and approved Protocol No. ORA-D-013-3 for issuance:



Signature

November 10, 2024
Date

Miriam Kidron, PhD
Chief Scientific Officer and Director
Oramed Ltd.

INVESTIGATOR SIGNATURE PAGE

I have read the attached protocol and agree that it contains all the necessary details for performing the study.

I will provide copies of the protocol and the Investigator's Brochure (IB), which were furnished to me by the Sponsor, to all members of the study team responsible to me who participate in the study. I will discuss this material with them to assure that they are fully informed regarding the study treatment, including the potential risks and side effects, and the conduct of the study.

Once the protocol has been approved by the Institutional Review Board (IRB), I will not modify this protocol without obtaining the prior approval of the Sponsor and the IRB. I will submit the protocol modifications and/or any informed consent form (ICF) modifications to the Sponsor and the IRB, and approval will be obtained before any modifications are implemented.

I understand the protocol and will work according to it, the principles of Good Clinical Practice [GCP; current International Council for Harmonisation (ICH) guidelines], and the Declaration of Helsinki (1964), including all amendments up to and including the October 2013 revision.

Principal Investigator Name	Signature	Date

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- E6(R2) GCP: Integrated Addendum to ICH E6(R1) (2018)

All key personnel (all individuals responsible for the design and conduct of this study) have completed GCP Training.

SYNOPSIS

Title	A Double-Blinded, Placebo-controlled, Double Dummy, Multi-center Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of ORMD-0801 in Subjects with Type 2 Diabetes Mellitus with Inadequate Glycemic Control on One to Three Glucose-lowering Agents
Protocol Number	ORA-D-013-3
Indication	Type 2 Diabetes Mellitus (T2DM)
Clinical Phase	Phase 3
Study Treatment	ORMD-0801 (insulin)
Dose	8 mg QD or 8 mg BID or 16 mg QD or matching placebo
Dosage Regimen	8 mg QD (one [8 mg × 1] capsule at night), or 8 mg BID (one [8 mg × 1] capsule at night and one [8 mg × 1] capsule 45 minutes before breakfast), or 16 mg QD (two [8 mg × 2] capsules at night)
Formulation	Soft gel capsule [SBTI, disodium EDTA, fish oil, aerosil, and Tween 80], recombinant human insulin
Mode of Administration	Oral
Primary Objective	To compare the efficacy of three doses of ORMD-0801 to placebo in improving glycemic control as assessed by A1C in inadequately controlled T2DM subjects on certain (one to three) glucose-lowering agents.
Secondary Objective	To assess the safety of repeat administration of ORMD-0801 in inadequately controlled T2DM subjects on one to three glucose-lowering agents.
Total Sample Size	Approximately 300 US-based adult male and female subjects with T2DM will be randomized in a 1:1:1:1 ratio to either ORMD-0801 8 mg QD (one [8 mg × 1] capsule) dosed at night (between 8 PM to midnight and no sooner than 1 hour after dinner), or to ORMD-0801 8 mg BID (one [8 mg × 1] capsule) dosed approximately 45 minutes (±15 minutes) before breakfast and at night (one [8 mg × 1] capsule dosed between 8 PM and midnight and no sooner than 1 hour after dinner), or to ORMD-0801 16 mg QD (two [8 mg × 2] capsules) dosed at night (between 8 PM to midnight and no sooner than 1 hour after dinner), or to matching placebo. In order to maintain the blind, a double dummy design will be used. All subjects will receive 1 capsule in the morning (1 × 8 mg ORMD-

	0801 or 1 matching placebo capsule) and 2 capsules at night (2 × 8 mg ORMD-0801 or 1 matching placebo capsule). It is anticipated that 75 subjects will be randomized to each arm of the study to complete 67 subjects in each arm.
Study Design	In this randomized, double-blind, double dummy, placebo-controlled study, approximately 300 eligible subjects with T2DM and inadequate control on at least one to three glucose-lowering agents will undergo an initial 4-week Screening Period. This will be followed by a 26-week Double-Blind Treatment Period, commencing with a safety Follow-up Visit four weeks after the completion of the trial. **Screening Period**: The Investigator will review the aim of the study, study procedures and potential risks and benefits. These subjects will then sign a written informed consent during the Screening Visit 1. They will be scheduled to return to the clinic 10 days prior to randomization for Screening Visit 2. At this visit, a CGM sensor will be placed with appropriate instructions by the study team for a 10-day blinded continuous glucose monitoring (CGM) data collection by the site. Subjects will then return to the clinic after 10 days (± 1-day) for removal of the CGM sensor. The subjects will be randomized to one of the four arms of the study treatment. **26-Week Double-Blind Treatment Period:** After the Screening Period, subjects will be randomized to 26 weeks of Double-Blind Treatment. In a double-blind, double dummy randomization scheme, subjects will be randomized to one of the following four treatment arms: 1. ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night). 2. ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night. 3. ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1

	hour after dinner and 1 matching placebo capsule in the morning. 4. Matching placebo. During the Double-Blind Treatment Period commencing at Week 0 (Visit 1, CGM removal), subjects will return to the clinic at Week 24 – Visit 5 (10 days prior to Week 26 for CGM application) and Week 26 – Visit 6 (CGM removal and end of Double-Blind Treatment Period visit). The visit requiring CGM application will occur 10 days prior to the CGM removal visit within ± 1-day window. **Safety Follow-up Visit:** All subjects completing the trial will return to the clinic in 4 weeks ± 3 days for a safety Follow-up Visit. Subjects withdrawing prematurely from the trial will have the early termination (ET) visit procedures completed. All patients will continue to be followed in accordance with ITT principles to avoid lost to follow-up and missing data. Throughout the course of the study, subjects will measure and record fasting blood glucose levels at least 2-3 times a week [self-monitored blood glucose (SMBG)] or when they experience any symptoms of hypoglycemia using a glucose meter. Subjects will be provided a paper diary at each clinic visit and trained to record information related to fasting blood glucose and description of hypoglycemic events: time and date of occurrence; symptoms experienced, if any; treatment given, if any; and specific circumstances. Subjects will be required to bring the paper diary at each clinic visit where data will be reviewed. **Rescue Visits and Medication:** During the Double-Blind Treatment Period background glucose-lowering dose regimens will be maintained, and further dose adjustments are discouraged unless clinically indicated as follows: Subjects will be eligible for rescue based on the following glycemic criteria: • From Day 1 (Visit 1) through Week 6 (Visit 2), if at least two fasting SMBG levels are > 270 mg/dL in the week preceding a

	visit are confirmed by a single central laboratory fasting glucose > 270 mg/dL. • From Week 6 (Visit 2) through Week 12 (Visit 3), if at least two fasting SMBG levels are > 240 mg/dL in the week preceding a visit are confirmed by a single central laboratory fasting glucose > 240 mg/dL. • From Week 12 (Visit 3) through Week 26 (Visit 6), if at least two fasting SMBG levels are > 220 mg/dL in the week preceding a visit are confirmed by a single central laboratory fasting glucose > 220 mg/dL. Rescue will allow subjects to remain in the study, remain on double-blind study medication, complete all visits until the end of the study, and thereby, contribute to efficacy, exposure, and safety data. Rescue medication will be prescribed in accordance with the study Investigator's usual standard of practice.
Primary Endpoint	• Change from baseline (Visit 1) in A1C at 26 weeks (Visit 6).
Secondary Endpoints	• Incidence of A1C < 7% at 26 weeks (Visit 6). • Change from baseline (Visit 1) in fasting plasma glucose (FPG) at 26 weeks (Visit 6). • Safety assessed by adverse event reporting including adverse events of special interest such as hypoglycemia.
Exploratory Endpoints	• Changes from baseline over time for A1C and FPG during the Double-Blind Treatment Period. • Change from baseline (Visit 1) in CGM-parameters at weeks 26. a) Mean Sensor Glucose, BG SD, BG CV, Time in range (TIR) — BG 70-180 mg/dL, BG 54-69 mg/dL, BG < 54 mg/dL, BG 181-250 mg/dL, and BG > 250 mg/dL. • Incidence of A1C < 8% at 26 weeks (Visit 6). • Incidence rate of subjects requiring glycemic rescue therapy and the time to rescue during the Double-Blind Treatment Period. • Change in weight from baseline during the Double-Blind Treatment Period. • Changes from baseline over time for C-peptide during the Double-Blind Treatment Period. • Changes from baseline over time in fasting insulin during the Double-Blind Treatment Period.

Duration of Participation	Subjects will participate in this study for approximately 30-34 weeks. • **Screening Period:** Screening Visit (Screen 1 and Screen 2); up to 4 weeks (Days -28 to -1) prior to the first dose of the study treatment • **Double-Blind Treatment Period:** Visit 1 (Week 0) – Visit 6 (Week 26) • **Safety Follow-up:** Visit 7 (Week 30)
Subject Selection Criteria	**Inclusion Criteria** 1. Male and female subjects aged ≥ 50 years. 2. Established diagnosis of T2DM for at least 6 months prior to Screening AND an A1C ≥ 7.2% but ≤ 10.0% at Screening. 3. On a stable dose of at least one and up to three of the following glucose-lowering agents: Metformin, sulfonylurea, DPP-4 inhibitor, SGLT-2 inhibitor, thiazolidinedione, insulin secretagogue, oral or injected GLP-1 receptor agonists, glucosidase inhibitor, or pramlintide (injected insulin is excluded) for a minimum of 3 months prior to Screening. 4. Body mass index (BMI) of ≤ 28 kg/m^2 at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening. 5. Renal function – eGFR ≥ 30 ml/min. 6. Females of childbearing potential must: a. Have a negative serum pregnancy test result at Screening. b. Agree to avoid becoming pregnant while receiving IP for at least 30 days prior to IP administration, during the entire study, and for 30 days following their last dose of IP. c. Agree to use an acceptable method of contraception at least 30 days prior to IP administration, during the entire study, and for 30 days following their last dose of IP. Acceptable methods of contraception are hormonal contraception (contraceptive pill or injection) **PLUS** an additional barrier method of contraception such as a diaphragm, condom, sponge, or spermicide. d. In the absence of hormonal contraception, double-barrier methods must be used which include a combination of any **two** of the following: diaphragm, condom, copper intrauterine device, sponge, or

	spermicide, and must be used for at least 30 days prior to administration of IP, during the entire study, and for 30 days following their last dose of IP. e. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are **not** acceptable methods of contraception. f. Females who are not of childbearing potential are defined as: i. Postmenopausal (defined as at least 12 months with no menses in women ≥ 45 years of age); OR ii. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR iii. Have a congenital or acquired condition that prevents childbearing. **Exclusion Criteria** Subjects with: 1. Type 1 diabetes by history. 2. Diabetes attributable to other secondary causes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant). 3. Treatment involving injected insulin within 3 months prior to Visit 1. 4. A history of > 2 episodes of severe hypoglycemia within 6 months prior to Screening. 5. A history of hypoglycemic unawareness. 6. A history of unstable angina or myocardial infarction within 6 months prior to Screening, New York Heart Association (NYHA) Grade 3 or 4 congestive heart failure (CHF), valvular heart disease, ventricular cardiac arrhythmia requiring

	treatment, pulmonary hypertension, cardiac surgery, coronary angioplasty, stroke, or transient ischemic attack (TIA) within 6 months prior to Screening. 7. A history of uncontrolled or untreated severe hypertension defined as systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg. A single repeat measurement will be permitted. 8. Renal dysfunction: eGFR < 30 mL/min. 9. A history of or active proliferative retinopathy requiring treatment. 10. Psychiatric disorders that, per Investigator judgment, may have impact on the safety of the subject or interfere with subject's participation or compliance in the study. 11. Laboratory abnormalities at Screening including: a. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or >1.5X the upper limit of normal; a single repeat test is allowable. b. Elevated liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)) > 3X the upper limit of normal; a single repeat test is allowable. c. Very elevated fasting triglyceride levels (> 600 mg/dL); a single repeat test is allowable. d. Any relevant abnormality that would interfere with the efficacy or the safety assessments during study treatment administration. 12. Positive history of active liver disease (other than non-alcoholic hepatic steatosis), primary biliary cirrhosis, or active symptomatic gallbladder disease. 13. Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus ribonucleic acid (RNA). 14. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma or carcinoma in situ of the cervix) within the past 5 years prior to baseline.

	15. Use of the following medications: a. History of use of any injectable insulin (greater than 7 days) within 6 months prior to Screening. b. Administration of thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to Screening. c. Use of oral, intravenous, or intramuscular steroids for one month prior to enrollment. Intra-articular and/or topical corticosteroids are not considered systemic. d. Concurrent use of medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and immunosuppressive or immunomodulating agents. Inhaled nasal steroids are permissible. 16. Known allergy to soy. 17. Involvement in a weight loss program and is not in the maintenance phase, or subject has started weight loss medication (e.g., orlistat or liraglutide) within 3 months prior to Screening. 18. Prior bariatric surgery. 19. Subject is pregnant or breast-feeding. 20. Subject is a user of recreational or illicit drugs or has had a recent history (within 1 year of Screening) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by > 3 drinks per day or > 14 drinks per week or binge drinking) at Screening. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during the 1 week prior to each visit. 21. Weight loss preparations either approved and marketed or used in OTC preparations except for GLP-1 used in the treatment of underlying diabetes. 22. Any condition or other factor (at the Investigator's discretion) that is deemed unsuitable for subject enrollment into the study.
Statistical Methods	**Power and Sample Size** The primary efficacy endpoint is the change from baseline in A1C at Week 26 (Visit 6). Based on subgroup results from a previous study, a drop in A1C of 0.6% is expected with a standard deviation of 1.1.

	Having 75 subjects per treatment group will ensure that the power will be at least 90% (with an alpha = 0.05). Assuming an approximate 10% drop out rate, 75 randomized subjects per treatment group would yield approximately 67 completers per treatment group. **Analysis Sets** The Safety Population will comprise all randomized patients who receive at least one dose of study medication. This population will be used for all summaries of patient accountability, demographic and baseline data, and safety information, including adverse event incidence and laboratory data. The Full Analysis Set (FAS) will consist of all randomized patients. This population will serve as the basis for all efficacy analyses. A Per Protocol Set (PPS) will consist of patients in the FAS who satisfy all enrollment criteria and are protocol compliant. Patients' data collected after the start of rescue medication will be excluded from the Per Protocol analyses. Criteria for excluding patients from the PPS will be finalized before unblinding the database. **Primary Efficacy Evaluation** The primary endpoint for this study is the change from baseline (Visit 1) in A1C at 26 weeks (Visit 6) for the active and placebo groups. Randomization will occur at Visit 1 (Week 0), where subjects will be stratified by Screening A1C values (A1C < 9.0 and A1C ≥ 9.0) and site (each site will be stratified independently). To preserve alpha, a hierarchical testing strategy will be used. The order of testing for active therapy versus placebo is: 1) ORMD-0801 16 mg once-daily, 2) ORMD-0801 8 mg twice daily and 3) ORMD-0801 8 mg once-daily. Change from baseline in A1C at 26 weeks will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment and site as categorical fixed effects and baseline A1C as a covariate. The treatment policy estimand is the primary estimand and will be estimated based on the FAS using Week 26 measurements. The primary statistical analysis will be a pattern mixed model using multiple imputation (MI) to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation.

	Intermittent missing data in an endpoint for subjects who complete treatment will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. This imputation will be done by the treatment group, using the MI procedure in SAS 9.4. The variables to be used in the imputation are treatment, corresponding baseline values and values observed at all double-blind visits. Missing data in an endpoint for subjects who prematurely discontinue treatment will be imputed from the observed data collected from subjects in the same treatment arm who prematurely discontinue treatment (retrieved dropouts). Intermittent missing data will be imputed using the Markov Chain Monte Carlo (MCMC) methodology. Once the data follows a monotone missing pattern, the monotone regression method will be used. If there are insufficient retrieved dropouts, the washout method will be used in which missing data in an endpoint from both treatment arms will be imputed using observed endpoint data from the placebo arm. When imputing missing values in the treatment arm, no intermediate endpoint values will be used, so only baseline data, baseline A1C and other covariates will be included in the model. When imputing missing values in the placebo arm, baseline data, intermediate endpoint values, and baseline A1C and other covariates will be included in the model. This imputation will be done using the MI procedure in SAS 9.4. The steps for conducting the primary analysis using the imputed datasets are: **Step 1**: Impute missing data as described above using PROC MI to form M complete datasets. M can vary and will be described in more detail in the Statistical Analysis Plan. **Step 2**: Analyze the change from baseline to Week 26 in A1C using an Analysis of Covariance (ANCOVA) model with treatment and site as categorical fixed effects and baseline A1C as a covariate for each of the M complete datasets.

	Step 3: Combine the results from each of the M complete datasets using Rubin's rule as implemented in PROC MIANALYZE in SAS 9.4. **Secondary Efficacy Evaluation** The incidence of A1C < 7% at 26 weeks will be analyzed as a binary endpoint using a g-computation estimator with site and baseline A1C as covariates.. The multiple imputation datasets used in the primary A1C analysis will be used to derive the incidence of A1C < 7%. Change from baseline in fasting plasma glucose at 26 weeks will be analyzed as a continuous variable in a manner consistent with the primary endpoint with the associated baseline response as a covariate in addition to baseline A1C. In order to maintain an overall Type I error rate of 0.05 a hierarchical approach will be used. The secondary endpoints will be tested in the following order: • Incidence of A1C < 7% at 26 weeks, and • Change from baseline in fasting plasma glucose at 26 weeks. **Exploratory Efficacy Evaluation** The exploratory efficacy endpoints will be evaluated for: • The primary estimand based on FAS using the Week 26 data regardless of adherence to randomized treatment and initiation of rescue medication. • The secondary estimand based on FAS using the Week 26 data censored after the start of rescue medication. Each of the Week 26 continuous efficacy endpoints will be analyzed as a continuous variable in a manner consistent with the primary endpoint with the associated baseline response as a covariate in addition to baseline A1C. Each of the Week 26 binary efficacy endpoints will be analyzed as a binary variable in a manner consistent with secondary efficacy binary endpoint.

	Other Statistical Efficacy Considerations The latest available measurement, at or prior to the randomization visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomization, the baseline value will be left missing. **Secondary Safety Evaluation** Change in hypoglycemia rates from baseline during the Double-Blind Treatment Period, and the Follow-up Visit will be provided using descriptive statistics (i.e., mean, median, range, and standard deviation). This analysis will use completed subjects (as predicting hypoglycemia rates could lead to an undercounting of events and a misinterpretation of the data). All AEs will be coded by Preferred Term using the MedDRA classification dictionary. The incidence of TEAEs will be summarized by treatment group, and by severity and relationship to study drug. Serious AEs (SAEs) and AEs leading to withdrawal from the study will be tabulated. **Other Safety Analysis** Other safety will be evaluated on the basis of vital signs, physical examinations, clinical laboratory assessments, prior and concomitant medications and supplements, and ECG findings. Changes from baseline in vital signs, physical examinations, weight, clinical laboratory values, and ECGs will be summarized by treatment group using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A1C or HbA1c	hemoglobin A1c
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGM	Continuous glucose monitoring
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ET	early termination
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
HOMA	The Homeostasis Model Assessment
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
IND	Investigational New Drug application
IRB	Institutional Review Board
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities

PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
RV	rescue visit
SAE	serious adverse event
SBP	systolic blood pressure
SBTI	soybean trypsin inhibitor
SOP	standard operating procedure
T1D	Type 1 diabetes
T2DM	Type 2 Diabetes Mellitus
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
WCBP	women of childbearing potential
WHO	World Health Organization

1 INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that has reached epidemic proportions in the United States, affecting almost 11.6% of the U.S. population in 2021 (Centers for Disease Control and Prevention, National Diabetes Statistics Report). Diabetes mellitus is a heterogenous disease (Mansour et al., 2021; Zaharia et al., 2019; Zou et al., 2019; Li Xia et al., 2020) defined by hyperglycemia (increased concentration of glucose in the blood) caused by defective insulin secretion and immune beta cell destruction (Type 1, T1D), resistance to insulin action (Type 2, T2DM), genetic and environmental influences or a combination of all of these. Diabetes mellitus leads to an increased risk of microvascular damage (retinopathy, nephropathy, and neuropathy), reduced life expectancy, increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life. According to the American Diabetes Association, Standards of Care in Diabetes (2023) include recommendations for lower hypertension and lipid thresholds, a fresh emphasis on sleep, weight loss, and physical activity, using social determinants of health to inform care design and delivery, and the use of tirzepatide and finerenone based on expanded FDA approvals.

The treatment goal for subjects with this disease is long-term glycemic control (over both fasting and non-fasting blood glucose levels), which has been demonstrated in both T1D and T2DM subjects to reduce the morbidities associated with uncontrolled glycemic levels (Diabetes Control and Complications Trial Research Group, 1993; Cleary et al., 2006; UK Prospective Diabetes Study Group, 1998a & 1998b). Typical options for glycemic control in subjects with T1D include two or more injections of insulin daily, with doses adjusted based on self-monitoring of blood glucose levels. Basal-bolus insulin therapy is an intensive insulin treatment that involves taking a combination of insulins (short- and long-acting insulin). Insulin replacement is accomplished by giving basal insulin and pre-prandial insulin. The basal insulin is either long acting (glargine or detemir) or intermediate-acting (NPH). Newer injectable insulins have been developed with once weekly durations of action (Insulin Icodec). The pre-prandial insulin is either rapid-acting (lispro, aspart, or glulisine) or short-acting (regular).

Glycemic control is measured by subject self-monitoring of blood glucose (SMBG), subject self-monitoring of interstitial glucose, and periodic blood tests for measurement of hemoglobin A1C (HbA1c or A1C). HbA1c levels reflect average glycemia over several months and therefore provide a surrogate for glycemic control (U.S. Food and Drug Administration, 2008). A consensus statement written by the American Diabetes Association and the European Association for the Study of Diabetes targets an HbA1c level of < 7% as an objective for nonpregnant adults, who do not have complicating factors, for the prevention of micro- and macrovascular disease (Nathan et al., 2009).

Subcutaneously administered insulin is highly effective at lowering glycemia and helping subjects achieve target HbA1c levels. However, analogous to some oral agents, over time insulin dosing increases because of associated weight gain and efficacy is diminished. Insulin has no overall

dose limit with respect to safety (except for hypoglycemia) and may provide an improved lipid profile. However, subcutaneously administered insulin requires daily injections and blood glucose monitoring and is associated with weight gain and an increased risk of hypoglycemia. Insulin is available as formulations with different pharmacokinetic (PK) and pharmacodynamic (PD) profiles (e.g., rapid, regular, intermediate, or long acting, or mixtures of these). These different formulations are used to tailor appropriate insulin regimens on a per subject basis (Nathan et al., 2006).

ORMD-0801 is based on Oramed's platform technology for the oral delivery of polypeptides, which includes a proprietary formulation of excipients to facilitate oral uptake by hindering proteolysis in the small intestine and facilitating translocation of peptides across the gut epithelial lining, and into the systemic circulation. The formulation for ORMD-0801 includes soybean trypsin inhibitor (SBTI) to hinder proteolysis, and disodium ethylenediaminetetraacetic acid (EDTA) to facilitate translocation. Fish oil provides omega-3 fatty acids. The enteric-coated capsules are designed to disintegrate in a pH- dependent manner in the small intestine. The initial indication for ORMD-0801 is to reduce fasting blood glucose in adult subjects with Type 2 diabetes mellitus with the objective of controlling the overall average glycemic level.

The potential advantage of oral insulin in the treatment of elevated fasting blood glucose as compared to subcutaneously administered insulin lies in the more physiological mechanism of delivery. Orally administered insulin, once transported across the gut wall, is ferried to the hepatic portal vein, mimicking the natural route of endogenous pancreatic insulin, and delivering the insulin directly to the intended site of action. In contrast, subcutaneously administered insulin reaches the liver through systemic circulation thereby requiring higher systemic levels of insulin in order to achieve the same effect. Thus, oral insulin administration (in combination with subcutaneously administered insulin) is expected to provide more physiological and improved control of blood glucose in Type 1 diabetes patients as well as in people with T2D. This will reduce their risk of hypoglycemia and may prevent weight gain. The PK/PD profile of ORMD-0801 is well-suited to the control of fasting blood glucose due to the delayed onset.

Oramed has completed sixteen Phase 1 clinical studies and twelve Phase 2 studies with ORMD-0801. Eleven of these studies were in T1DM patients (n = 133) and seven in T2DM patients (n = 655). The remaining studies were conducted in healthy volunteers (n = 111).

Additionally, Oramed has also conducted one Phase 2b study, two Phase 3 studies in patients with type 2 diabetes, and one Phase 2 study in patients with type 2 diabetes with NASH. The two Phase 3 studies were terminated early for not meeting their primary endpoint.

The Oramed Phase 3 study was designed as a 57-week study with a Double-Blind Treatment Period and the Double-Blind Treatment Extension Period, each lasting for approximately 26 weeks. The safety data in this study as monitored by an independent data safety monitoring committee (DSMB) revealed that ORMD-0801 was well tolerated in T2DM patients and had a

safety profile that was similar to placebo. Post the primary and secondary analyses, subjects were classed into four subgroups based on their BMI. The low BMI ≤ 28.123 subgroup was further investigated to examine the effect of age (≥ 50 years and ≥ 58 years) on A1C and fasting plasma glucose. Subjects that received 8 mg QD and 8 mg BID demonstrated a significant reduction of 0.447 and 0.569, respectively, in the placebo-adjusted mean A1C (%) within the low BMI (≤ 28.123) subgroup at 26 weeks. Additionally, subjects with a low BMI ≤ 28.123 and age ≥ 50 years showed a significant placebo-adjusted mean decrease of 0.833 in 8 mg BID group (p-Value = 0.0166) at 26 weeks.

These crucial findings prove that the ORMD-0801 8 mg insulin per dose administered once and twice daily orally is safe and point towards the potential beneficial effects of ORMD-0801 in low BMI subjects of age ≥ 50 years diagnosed with T2DM.

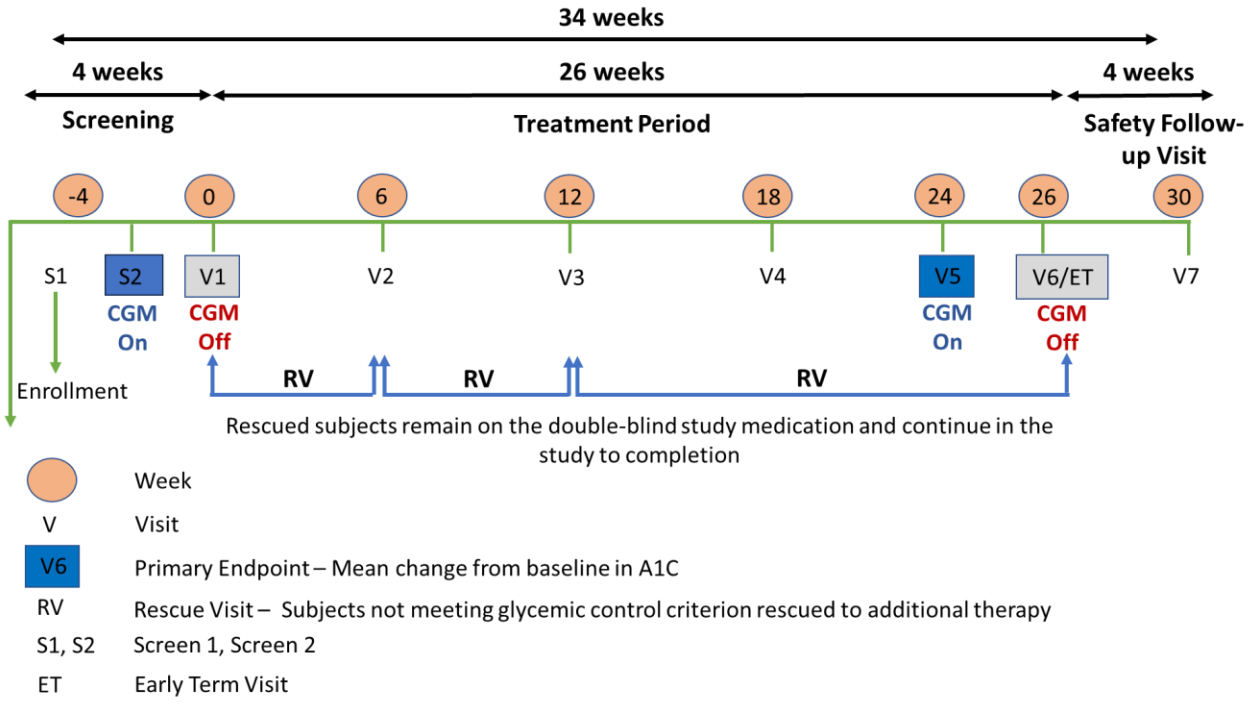
2 STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoint**
1. To compare the efficacy of two doses of ORMD-0801 to placebo in improving glycemic control as assessed by A1C in inadequately controlled T2DM subjects on certain (one to three) glucose-lowering agents.	1. Change from baseline (Visit 1) in A1C at 26 weeks (Visit 6).
Secondary Objective	**Secondary Endpoints**
1. To assess the safety of repeat administration of ORMD-0801 in inadequately controlled T2DM subjects on one to three glucose-lowering agents.	1. Incidence of A1C < 7% at 26 weeks (Visit 6). 2. Change from baseline (Visit 1) in fasting plasma glucose (FPG) at 26 weeks (Visit 6). 3. Safety assessed by adverse event reporting including adverse events of special interest such as hypoglycemia.
	Exploratory Endpoints
	1. Changes from baseline over time for A1C and FPG during the Double-Blind Treatment Period. 2. Change from baseline (Visit 1) in CGM-parameters at weeks 26. a) Mean Sensor Glucose, BG SD, BG CV, Time in range (TIR)—BG 70-180 mg/dL, BG 54-69 mg/dL, BG < 54 mg/dL, BG 181-250 mg/dL, and BG > 250 mg/dL. 3. Incidence of A1C < 8% at 26 weeks (Visit 6). 4. Incidence rate of subjects requiring glycemic rescue therapy and the time to rescue during the Double-Blind Treatment Period. 5. Change in weight from baseline during the Double-Blind Treatment Period. 6. Changes from baseline over time for C-peptide during the Double-Blind Treatment Period. 7. Changes from baseline over time in fasting insulin during the Double-Blind Treatment Period.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

In this randomized, double-blind, double dummy, placebo-controlled study, approximately 300 eligible subjects with T2DM and inadequate control on at least one to three glucose-lowering agents will undergo an initial 4-week Screening Period. This will be followed by a 26-week Double-Blind Treatment Period, commencing with a safety Follow-up Visit four weeks after the completion of the trial.



3.1.1 Screening Period

The Investigator will review the aim of the study, study procedures and potential risks and benefits. These subjects will then sign a written informed consent during the Screening Visit 1 (Screen 1) following which various study procedures will be performed (refer to Table 2). They will be scheduled to return to the clinic 10 days prior to randomization for Screening Visit 2 (Screen 2). At this visit, a CGM sensor will be placed with appropriate instructions by the study team for a 10-day blinded continuous glucose monitoring (CGM) data collection by the site. Subjects will then return to the clinic after 10 days (± 1-day) for removal of the CGM sensor. The subjects will be randomized to one of the four arms of the study treatment.

3.1.2 Treatment Period

After the Screening Period, subjects will be randomized to 26 weeks of Double-Blind Treatment.

In a double-blind, double dummy randomization scheme, subjects will be randomized to one of the following four treatment arms:

1. ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).

2. ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.

3. ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.

4. Matching placebo.

During the Double-Blind Treatment Period commencing at Week 0 (Visit 1, CGM removal), subjects will return to the clinic at Week 24 – Visit 5 (10 days prior to Week 26 for CGM application) and Week 26 – Visit 6 (CGM removal and end of Double-Blind Treatment Period visit).

The visit requiring CGM application will occur 10 days prior to the CGM removal visit within ± 1-day window.

3.1.3 Safety Follow-up/End of Study

All subjects completing the trial will return to the clinic in 4 weeks ± 3 days for a safety Follow-up Visit. Study procedures and assessments will be performed per Table 2.

Subjects withdrawing prematurely from the trial will have the early termination (ET) visit procedures completed. All patients will continue to be followed in accordance with ITT principles to avoid lost to follow-up and missing data.

Throughout the course of the study, subjects will measure and record fasting blood glucose levels at least 2-3 times a week [self-monitored blood glucose (SMBG)] or when they experience any symptoms of hypoglycemia using a glucose meter. Subjects will be provided a paper diary at each clinic visit and trained to record information related to fasting blood glucose and description of hypoglycemic events: time and date of occurrence; symptoms experienced, if any; treatment given,

if any; and specific circumstances. Subjects will be required to bring the paper diary at each clinic visit where data will be reviewed.

3.1.4 Rescue Visits and Medication

During the Double-Blind Treatment Period, background glucose-lowering dose regimens will be maintained, and further dose adjustments are discouraged unless clinically indicated as follows:

Subjects will be eligible for rescue based on the following glycemic criteria:

- From Day 1 (Visit 1) through Week 6 (Visit 2), if at least two fasting SMBG levels are > 270 mg/dL in the week preceding a visit are confirmed by a single central laboratory fasting glucose > 270 mg/dL.
- From Week 6 (Visit 2) through Week 12 (Visit 3), if at least two fasting SMBG levels are > 240 mg/dL in the week preceding a visit are confirmed by a single central laboratory fasting glucose > 240 mg/dL.
- From Week 12 (Visit 3) through Week 26 (Visit 6), if at least two fasting SMBG levels are > 220 mg/dL in the week preceding a visit are confirmed by a single central laboratory fasting glucose > 220 mg/dL.

Rescue will allow subjects to remain in the study, remain on double-blind study medication, complete all visits until the end of the study, and thereby, contribute to efficacy, exposure, and safety data. Rescue medication will be prescribed in accordance with the study Investigator's usual standard of practice.

3.2 Screening Period (4 Weeks prior to Visit 1)

The Screening Period can last for up to 4 weeks and will consist of Screening Visit 1 (Screen 1) and Screening Visit 2 (Screen 2).

3.2.1 Screen 1

At Screen 1, potential subjects will be given a detailed oral presentation describing the nature, purpose, risks, and requirements of the study and will receive detailed written information. Subjects will be given ample time to consider participation and ask questions that will be adequately addressed by site personnel.

Once the subject is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study informed consent form (ICF) (refer to Section 11.2.4 for further detail regarding the ICF). The Investigational Site personnel obtaining written consent from the subject will also sign the form to confirm their consent has been obtained.

Once signed, the Investigator will retain the original ICF for the subject's study records and provide the subject with a signed copy. The Investigator will verify that informed consent has been

obtained from each subject prior to enrollment into the study and prior to the subject undergoing any study-related procedures.

Subjects will report to the clinic in the morning following a 10-hour fast. Screening activities after obtaining informed consent will be conducted and consist of the following:

- Review of inclusion and exclusion criteria.
- Collection of demographic data (sex, age, race, and ethnicity).
- Completion of medical history, including tobacco, alcohol, caffeine, and drug use.
- Review of prior and concomitant medications and supplements.
- Physical examination.
- 12-Lead electrocardiogram (ECG).
- Measurement of height and weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical labs including hematology, serum chemistry (including A1C, C-peptide, CRP, and serum thyrotropin/TSH), urinalysis, and serum lipid panel (see Section 6.1.5.1 for list of tests).
    - Serology (Hepatitis B, Hepatitis C, and HIV).
    - Urine drug screen.
    - Serum (hCG) pregnancy test (women of childbearing potential/WCBP only).
    - FSH test (women that are not of childbearing potential, if applicable).
    - Plasma glucose.
    - Insulin for HOMA estimate.
- Remind eligible subjects to return to the clinic for Screen 2 (10 days prior to randomization).

For subjects who meet eligibility criteria based on the screening assessments, instruction will be provided on the following:

- The use of adequate contraceptive methods (see Section 4.1) for the duration of the study (Screening through Follow-up) and for 30 days following their last dose of IP.
- Avoid use of concomitant medication unless deemed necessary by the Investigator and avoid prohibited medications as defined in Section 5.6.
- Maintenance of usual dietary habits and avoidance of drastic changes, such as a conversion to a vegetarian diet.
- Refrain from any unusual or unaccustomed vigorous exercise during the study.
- Restraint from excessive alcohol use or binge drinking during the study, and restraint from drinking alcohol from 72 hours prior to all study visits.
- Restraint from excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) during the study.

- Refrain from weight loss preparations either approved and marketed or used in OTC preparations except for GLP-1 used in the treatment of underlying diabetes.

3.2.2 Screen 2 [10 Days prior to Randomization at Week 0 (Visit 1) ± 1-day]

At Screen 2, eligible subjects will report to the clinic in the morning, 10 days prior to randomization [Week 0 (Visit 1)] and the following activities will be performed:

- Review of inclusion and exclusion criteria.
- Review of prior and concomitant medications and supplements.
- CGM application.
- Dispense a paper diary and train subjects to record information related to fasting blood glucose levels at least 2-3 times a week and capture events of hypoglycemia: exact time and date of occurrence; symptoms experienced and interventions, if any, such as administration of rescue medication; and specific circumstances. Remind subjects to bring the diary at each clinic visit.
- Remind subjects to arrive fasting for Visit 1 in 10 days.

3.2.3 Screen Failure

A screen failure is defined as a subject who has signed the ICF, does not meet all the entry criteria outlined in Section 4 of this protocol (note that this criteria includes assessments through Visit 1) and was not randomized to receive the study treatment (active or placebo). The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents and on the Screening log. Screen failure subjects will have only their consent, demographic and reason for screen failing (including, where applicable, the unmet inclusionary or exclusionary criteria) data entered into the electronic data capture (EDC) system, unless an adverse event was responsible for the subject's screen failure, in which case all electronic case report form (eCRF) data collected for that subject during the screening process will be entered into the EDC system.

3.3 **Treatment Period (Week 0, Visit 1 – Week 26, Visit 6)**

3.3.1 Visit 1 (Week 0 ± 1 day)

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medication. The following activities will be performed:

- Review of inclusion and exclusion criteria.
- Review of concomitant medications and supplements.
- Physical examination.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:

  - Clinical labs including hematology, serum chemistry (including A1C [Pre-dose] and CRP), and serum lipid panel (see Section 6.1.5.1 for list of tests).
  - Urine pregnancy test (WCBP only).
  - Plasma glucose.
- Removal of CGM device and CGM data collection.
- Collect and review paper diary for completeness of fasting blood glucose level entries and events of hypoglycemia (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Subjects will be randomized to one of the following four treatment arms:
  - ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).
  - ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
  - ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
  - Matching placebo.
- Subjects will be administered morning treatment dose in clinic.
- Dispense blinded treatment medication with instructions for administration.
- Record adverse events following administration of first treatment dose, if applicable.
- Remind subjects to arrive fasting for Visit 2 in 6 weeks.

3.3.2 Visit 2 (Week 6 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medication. The following activities will be performed:

- Review of concomitant medications and supplements.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collect fasted blood sample for plasma glucose.
- Collect fasted blood sample for A1C measurement.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Collection of unused blinded medication.
- Subjects will receive one of the following four treatments:

  - ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).
  - ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
  - ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
  - Matching placebo.
- Subjects will be administered morning treatment dose in clinic.
- Dispense blinded treatment medication with instructions for administration.
- Assess for rescue.
- Record adverse events.
- Remind subjects to arrive fasting for Visit 3 in 6 weeks.

3.3.3 Visit 3 (Week 12 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medication. The following activities will be performed:

- Review of concomitant medications and supplements.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
  - Clinical labs including hematology, serum chemistry (with A1C, C-peptide, and CRP), and serum lipid panel (see Section 6.1.5.1 for list of tests).
  - Urine pregnancy test (WCBP only).
  - Plasma glucose.
  - Insulin for HOMA estimate.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Collection of unused blinded medication.
- Subjects will receive one of the following four treatments:
  - ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).

  - ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
  - ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
  - Matching placebo.
- Subjects will be administered morning treatment dose in clinic.
- Dispense blinded treatment medication with instructions for administration.
- Assess for rescue.
- Record adverse events.
- Remind subjects to return to the clinic for Visit 4 in 6 weeks.

3.3.4 Visit 4 (Week 18 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medication. The following activities will be performed:

- Review of concomitant medications and supplements.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collect fasted blood sample for plasma glucose.
- Collect fasted blood sample for A1C measurement.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Collection of unused blinded medication.
- Subjects will receive one of the following four treatments:
  - ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).
  - ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
  - ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
  - Matching placebo.

- Subjects will be administered morning treatment dose in clinic.
- Dispense blinded treatment medication with instructions for administration.
- Assess for rescue.
- Record adverse events.
- Remind subjects to return to the clinic for Visit 5 in 6 weeks.

3.3.5 Visit 5 (Week 24, Day 172 ± 3 days)

Subjects will report to the clinic in the morning and the following activities will be performed:

- Review of concomitant medications and supplements.
- Measurement of vital signs (SBP/DBP and heart rate).
- CGM application.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Collection of unused blinded medication.
- Subjects will receive one of the following four treatments:
    - ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).
    - ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
    - ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
    - Matching placebo.
- Subjects will be administered morning treatment dose in clinic.
- Dispense blinded treatment medication with instructions for administration.
- Assess for rescue.
- Record adverse events.
- Remind subjects to arrive fasting for Visit 6 in 10 days.

3.3.6 Visit 6 (Week 26, Day 182 ± 1-day) / Early Termination (ET) Visit

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medication. The following activities will be performed:

- Review of concomitant medications and supplements.

- Physical examination.
- 12-Lead ECG.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical labs including hematology, serum chemistry (with A1C, C-peptide, and CRP), urinalysis, and serum lipid panel (see Section 6.1.5.1 for list of tests).
    - Urine pregnancy test (WCBP only).
    - Plasma glucose.
    - Insulin for HOMA estimate.
- Removal of CGM device and CGM data collection.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Collection of unused blinded medication.
- Assess for rescue.
- Record adverse events.
- Remind/instruct subjects to report to the site any SAEs that occur within 30 days following the last dose of IP.
- Remind subjects to arrive fasting for Safety Follow-up Visit 7 in 4 weeks.

3.4 Safety Follow-up Visit

3.4.1 Visit 7 (Week 30 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast and the following activities will be performed:

- Review of concomitant medications and supplements.
- Physical examination.
- 12-Lead ECG.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical labs including hematology, serum chemistry (with A1C, C-peptide, and CRP), and serum lipid panel (see Section 6.1.5.1 for list of tests).
    - Urine pregnancy test (WCBP only).
    - Plasma glucose.
    - Insulin for HOMA estimate.

- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events (if applicable).
- Record hypoglycemic events as an AE of special interest (if applicable).
- Record adverse events.
- Ask subjects about any SAEs that occurred within 30 days following the last dose of IP.
- Discharge from study.

3.5 Rescue Visit (RV)

Subjects will be eligible for rescue based on the following glycemic criteria shown below in Table 1:

Table 1: Rescue Visit Criteria

Week	Criteria
From Day 1 (Visit 1) through Week 6 (Visit 2)	Fasting SMBG > 270 mg/dL*
From Week 6 (Visit 2) through Week 12 (Visit 3)	Fasting SMBG > 240 mg/dL*
From Week 12 (Visit 3) through Week 26 (Visit 6)	Fasting SMBG > 220 mg/dL*
*At least two elevated fasting SMBG levels in a week preceding a visit are confirmed by a single central laboratory report.	

If deemed eligible for rescue, subjects will report to the clinic in the morning following a 10-hour fast and the following activities will be performed:

- Review of concomitant medications and supplements.
- Physical examination.
- 12-Lead ECG.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical labs, including hematology, serum chemistry (with A1C), and serum lipid panel (see Section 6.1.5.1 for list of tests).
    - Plasma glucose.
- Collect and review paper diary for completeness of fasting blood glucose level entries and hypoglycemic events.
- Dispense a new paper diary.
- Record hypoglycemic events as an AE of special interest (if applicable).
- Record adverse events.

- After completing the Rescue Visit, subjects will continue in the study to completion. Remind subjects to return to the clinic in a fasting or a non-fasting state depending on their next visit.

3.6 Schedule of Events

Table 2 below describes the daily schedule of events from Screening through Safety Follow-up Visit.

Table 2: Daily Schedule of Events from Screening through Safety Follow-up Visit

	Screening		Treatment Period						Safety Follow-up Visit	Rescue
Visit[1]	**Screen 1**	**Screen 2[9]**	**1[2]**	**2**	**3**	**4**	**5[9]**	**6[2]**	**7**	**RV**
Week	**-4 weeks**		**0**	**6**	**12**	**18**	**24 (Day 172)**	**26/ET[8] (Day 182)**	**30**	**Variable**
Informed Consent	X									
Inclusion/Exclusion	X	X	X							
Demographics (sex, age, race, and ethnicity)	X									
Medical History	X									
Prior and Concomitant Medications and Supplements[3]	X	X	X	X	X	X	X	X	X	X
Physical Examination[4]	X		X					X	X	X
12-Lead ECG	X							X	X	X
Height and Weight[5]	X		X		X	X		X	X	X
Vital Signs[6]	X		X	X	X	X	X	X	X	X
Chemistry, Hematology, and Serum Lipid Panel	X		X		X			X	X	X
Urinalysis	X							X		
Serology (Hep B, C, and HIV)	X									
Urine Drug Screen	X									
Pregnancy Test/FSH[7]	X		X		X			X	X	
C-peptide, CRP, and TSH[10]	X		X		X			X	X	
Fasting Plasma Glucose	X		X	X	X	X		X	X	X

	Screening		Treatment Period						Safety Follow-up Visit	Rescue
Visit[1]	**Screen 1**	**Screen 2[9]**	**1[2]**	**2**	**3**	**4**	**5[9]**	**6[2]**	**7**	**RV**
Week	**-4 weeks**		**0**	**6**	**12**	**18**	**24 (Day 172)**	**26/ET[8] (Day 182)**	**30**	**Variable**
A1C	X		X (Pre-dose)	X	X	X		X	X	X
Fasting Insulin[11]	X				X			X	X	
Randomization			X							
CGM On/Off (CGM data collection)		On	Off				On	Off		
Dispense paper diary and Train on Use; SMBG/Nutrition/Hypoglycemia Symptom Training[12]		X								
Collect and Review paper diary and assess for Hypoglycemic events; Dispense new paper diary[13]			X	X	X	X	X	X	X	X
Question about hypoglycemic events as an AE of special interest			X	X	X	X	X	X	X	X
Dispense/Collect Blinded Medication			X	X	X	X	X	X		
In-clinic Dosing			X	X	X	X	X			
Assess for Rescue				X	X	X	X	X		
Adverse Events[14]			X	X	X	X	X	X	X	X

[1] All non-screening Visits except Visits 1 and 6 have a visit window of ± 3 days.

[2] Visits 1 and 6 for CGM removal must follow Visits Screen 2 and 5, respectively for CGM application by 10 days (± 1-day).

[3] Prior medications and supplements will be reviewed at Screening (Screen 1 and 2) and Visit 1. Concomitant medications and supplements will be reviewed as indicated.

[4] Physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological examination.

[5] Height will be measured at Screening (Screen 1) only. Weight will be measured as indicated.

[6] Heart rate and blood pressure.

[7] For women of childbearing potential (WCBP) only: Serum hCG test will be performed at Screening (Screen 1), and urine pregnancy testing will be performed at Visits 1, 3, 6, 7, and ET (if applicable); For women that are not of childbearing potential: Serum FSH test will be performed at Screening (Screen 1) only.

[8] Subjects withdrawing prematurely from the trial at any visit will have the ET visit procedures completed.

[9] Each visit requiring CGM application (Visits Screen 2 and 5) will occur 10 days prior to CGM removal.

[10] TSH at Screening (Screen 1) only; C-Peptide at Screening (Screen 1) and Visits 3, 6, 7, and ET Visit (if applicable); and CRP at Screening (Screen 1) and Visits 1, 3, 6, 7, and ET Visit (if applicable).

[11] Fasting insulin will be used to determine Homeostasis Model Assessment (HOMA) estimates.

[12] Subjects will be dispensed a paper diary and trained to record information related to fasting blood glucose (at least 2-3 times a week) and events of hypoglycemia: exact time and date of occurrence; symptoms experienced and interventions, if any, such as administration of rescue medication; and specific circumstances.

[13] Subject diaries will be dispensed and collected at each visit. Subjects will be reminded to record fasting blood glucose values in their paper diary.

[14] Adverse events to be captured following treatment administration at Visit 1/Randomization. Remind/instruct subjects to report to the site any SAEs that occur within 30 days following the last dose of IP.

4 STUDY SUBJECT SELECTION

4.1 Inclusion Criteria

1. Male and female subjects aged ≥ 50 years.
2. Established diagnosis of T2DM for at least 6 months prior to Screening AND an A1C ≥ 7.2% but ≤ 10.0% at Screening.
3. On a stable dose of at least one and up to three of the following glucose-lowering agents: Metformin, sulfonylurea, DPP-4 inhibitor, SGLT-2 inhibitor, thiazolidinedione, insulin secretagogue, oral or injected GLP-1 receptor agonists, glucosidase inhibitor, or pramlintide (injected insulin is excluded) for a minimum of 3 months prior to Screening.
4. Body mass index (BMI) of ≤ 28 kg/m^2 at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening.
5. Renal function – eGFR ≥ 30 ml/min.
6. Females of childbearing potential must:
    a. Have a negative serum pregnancy test result at Screening.
    b. Agree to avoid becoming pregnant while receiving IP for at least 30 days prior to IP administration, during the entire study, and for 30 days following their last dose of IP.
    c. Agree to use an acceptable method of contraception at least 30 days prior to IP administration, during the entire study, and for 30 days following their last dose of IP. Acceptable methods of contraception are hormonal contraception (contraceptive pill or injection) **PLUS** an additional barrier method of contraception such as a diaphragm, condom, sponge, or spermicide.
    d. In the absence of hormonal contraception, double-barrier methods must be used which include a combination of any **two** of the following: diaphragm, condom, copper intrauterine device, sponge, or spermicide, and must be used for at least 30 days prior to administration of IP, during the entire study, and for 30 days following their last dose of IP.
    e. Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are **not** acceptable methods of contraception.
    f. Females who are not of childbearing potential are defined as:
        i. Postmenopausal (defined as at least 12 months with no menses in women ≥ 45 years of age); OR

ii. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR

iii. Have a congenital or acquired condition that prevents childbearing.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria must be excluded from the study:

1. Type 1 diabetes by history.
2. Diabetes attributable to other secondary causes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).
3. Treatment involving injected insulin within 3 months prior to Visit 1.
4. A history of > 2 episodes of severe hypoglycemia within 6 months prior to Screening.
5. A history of hypoglycemic unawareness.
6. A history of unstable angina or myocardial infarction within 6 months prior to Screening, New York Heart Association (NYHA) Grade 3 or 4 congestive heart failure (CHF), valvular heart disease, ventricular cardiac arrhythmia requiring treatment, pulmonary hypertension, cardiac surgery, coronary angioplasty, stroke, or transient ischemic attack (TIA) within 6 months prior to Screening.
7. A history of uncontrolled or untreated severe hypertension defined as systolic blood pressure above or equal to 160 mmHg and/or diastolic blood pressure above or equal to 100 mmHg. A single repeat measurement will be permitted.
8. Renal dysfunction: eGFR < 30 mL/min.
9. A history of or active proliferative retinopathy requiring treatment.
10. Psychiatric disorders that, per Investigator judgment, may have impact on the safety of the subject or interfere with subject's participation or compliance in the study.
11. Laboratory abnormalities at Screening including:

    a. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or >1.5X the upper limit of normal; a single repeat test is allowable.

    b. Elevated liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)) > 3X the upper limit of normal; a single repeat test is allowable.

    c. Very elevated fasting triglyceride levels (> 600 mg/dL); a single repeat test is allowable.

    d. Any relevant abnormality that would interfere with the efficacy or the safety assessments during study treatment administration.

12. Positive history of active liver disease (other than non-alcoholic hepatic steatosis), primary biliary cirrhosis, or active symptomatic gallbladder disease.
13. Positive results for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C virus ribonucleic acid (RNA).
14. Patient has active or history of neoplastic disease (except for adequately treated non-invasive basal cell and/or squamous cell carcinoma or carcinoma in situ of the cervix) within the past 5 years prior to baseline.
15. Use of the following medications:
    a. History of use of any injectable insulin (greater than 7 days) within 6 months prior to Screening.
    b. Administration of thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to Screening.
    c. Use of oral, intravenous, or intramuscular steroids for one month prior to enrollment. Intra-articular and/or topical corticosteroids are not considered systemic.
    d. Concurrent use of medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and immunosuppressive or immunomodulating agents. Inhaled nasal steroids are permissible.
16. Known allergy to soy.
17. Involvement in a weight loss program and is not in the maintenance phase, or subject has started weight loss medication (e.g., orlistat or liraglutide) within 3 months prior to Screening.
18. Prior bariatric surgery.
19. Subject is pregnant or breast-feeding.
20. Subject is a user of recreational or illicit drugs or has had a recent history (within 1 year of Screening) of drug or alcohol abuse or dependence. (Note: Alcohol abuse includes heavy alcohol intake as defined by > 3 drinks per day or > 14 drinks per week or binge drinking) at Screening. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during the 1 week prior to each visit.
21. Weight loss preparations either approved and marketed or used in OTC preparations except for GLP-1 used in the treatment of underlying diabetes.
22. Any condition or other factor (at the Investigator’s discretion) that is deemed unsuitable for subject enrollment into the study.

4.3 Subject and Trial Discontinuation

Subjects may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

Within the provisions of informed consent and good clinical judgment with respect to safety, every attempt will be made to have subjects complete the study. Reasons for subject discontinuation include, but are not limited to the following:

1. Subject experiences an AE that in the judgement of the Investigator poses a significant risk to the subject for continued participation in the study.
2. Subject uses a prohibited medication (listed in Section 5.6) that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of the study.
3. Subject becomes pregnant.
4. Significant protocol violation or noncompliance on the part of the subject or the Investigator.
5. Intercurrent illness requires treatment not consistent with the protocol requirements, or intercurrent illness and the associated treatment poses a significant risk to the subject for continued participation in the study in the judgment of the Investigator.
6. Episodes of hypoglycemia not responsive to changes in diet or dose regimen (See Section 7.3.1).
7. Subject meets one of the exclusion criteria during the study.
8. Subject wishes to withdraw for any reason.
9. Sponsor elects to end the study or the Investigational Site elects to end the study at their site.
10. Any other reason in the judgment of the Investigator that poses unacceptable risk to the subject.

Subjects who withdraw from the study prior to treatment may be replaced. Subjects who are withdrawn and have received at least one treatment will not be replaced.

Except in cases of emergency, the Investigator should consult with the Sponsor and the Medical Monitor before removing the subject from the study. In some circumstances, it may be necessary to temporarily interrupt treatment because of AEs that may have an unclear relationship to study treatment. The Investigator should obtain approval from the Sponsor and Medical Monitor before restarting study treatments that were temporarily discontinued for an AE.

If a subject discontinues the study prior to completion, the date the subject is withdrawn and the reason for discontinuation will be recorded in the source documents and eCRF. Although a subject will not be obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject’s rights.

All subjects who are randomized and treated (i.e., received any amount of study treatment) will be included in the safety analyses. Thus, every effort will be made to contact any subject who fails to attend any follow-up appointments/contacts, to ensure that he/she is in satisfactory health. If a subject withdraws from the study as a result of meeting discontinuation criteria (Section 4.3) after the start of study treatment administration, reasonable efforts should be made to have the subject return for the early termination evaluations (Section 3.3.7). Any subject withdrawn due to a suspected study treatment-related AE should be followed until resolution or stabilization of the event.

If a subject becomes pregnant, study treatment will be discontinued immediately. The subject will be followed until delivery or other termination of pregnancy for outcome.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation among involved parties. The Investigator will notify the IRB in writing of a premature termination of a study or closure of Investigational Site and will send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, GCP violations, slow recruitment/low enrollment, or change in development plans for the study treatment.

It is of great importance to follow all patients, including those who discontinue study drug prematurely, for safety and efficacy measurements until the end of the study as this will help prevent missing data in statistical analyses and ensure that the study can reliably meet its objectives.

- Site investigators will be trained regarding the importance of retention and steps to prevent missing data.
- The consent forms will include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early.
- Several approaches will be implemented to retain patients who fail to actively maintain contact with the investigator. These approaches include but may not be limited to telephone calls, e-mails and offering transportation to the clinic.

If either of the criteria listed below is met, enrollment of new subjects and dosing of ongoing subjects will be temporarily stopped. The Investigator, Sponsor, and the Medical Monitor will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such

findings will be submitted for review and approval by the IRB and FDA prior to re-starting the trial.

1. A death within 30 days after study treatment administration where there is a reasonable possibility that the drug caused the event.
2. Two Grade 4 AEs where there is a reasonable possibility that the study treatment caused the events.

5 STUDY TREATMENT

5.1 Description of Investigational Drug

Active:

Code Name: ORMD-0801 (insulin)

Dosage Form: 8 mg QD (one [8 mg × 1] capsule at night), or 8 mg BID (one [8 mg × 1] capsule at night and one [8 mg × 1] capsule 45 minutes before breakfast), or 16 mg QD (two [8 mg × 2] capsules at night) administered daily.

Strength: 8 mg insulin per capsule.

Description: Recombinant human insulin, soft gel capsule composed of SBTI, disodium EDTA, fish oil, aerosil, and Tween 80.

Placebo control (No Insulin):

Disodium EDTA, SBTI, fish oil, aerosil, and Tween 80, identical in appearance to ORMD-0801.

5.1.1 Packaging and Labeling

All study medication will be shipped in pre-prepared kits to be allocated to subjects by the interactive web-based response system (IWRS) based on study period, randomization and individual dose regimen achieved. Sufficient study medication will be distributed to cover the time between visits. This medication should be kept at the site, stored, and locked in a refrigerated drug room prior to distribution to the subject. The Investigational Site pharmacist or designee will be responsible for dispensing the appropriate study period treatment based on the randomization schedule.

Shipments of study medication (active and placebo) for the Double-Blind Treatment Period will be received in blinded packages. Study medication will be dispensed to the site with instructions for when treatment can be administered. Medication containers and any unused capsules will be

retained at the study site after the treatment phase of the trial is complete. Unused study medication will be returned to the depot for destruction.

The treatment packages will be labeled with the following information:

- Study number
- Kit No./Bottle ID
- Dosage Form/Content
- Directions for use, including route of administration
- Number of capsules in package
- Storage conditions
- Instructions to "keep out of reach of children"
- Caution: New Drug – Limited by Federal (or United States) law to investigational use
- Name of Sponsor

A separate label with identical information will be provided with the label on the package for drug accountability purposes.

5.1.2 Storage and Handling

All study treatment must be kept in an appropriate, secure area to prevent unauthorized access. The study treatment is to be shipped under refrigerated conditions and stored in the original packaging at controlled temperature (36 to 46°F; 2 to 8°C). Excessive humidity should be avoided. Storage conditions will be monitored, and appropriate monitoring logs maintained as source data. Deviations from the established temperature, as well as the occurrence of excessive humidity, should be documented and the Sponsor should be notified. Study treatment should be handled using proper procedures as defined by Investigational Site standard operating procedures (SOPs) for Investigational Drugs. Unused study medication will be returned to the depot for destruction.

5.2 Randomization

In this randomized, double-blind, double dummy, placebo-controlled study, approximately 300 US-based adult male and female subjects with T2DM and inadequate glycemic control on at least one and up to three glucose-lowering agents will be randomized in a 1:1:1:1 ratio to either ORMD-0801 8 mg QD (one [8 mg × 1] capsule) dosed at night (between 8 PM to midnight and no sooner than 1 hour after dinner), or to ORMD-0801 8 mg BID (one [8 mg × 1] capsule) dosed approximately 45 minutes (±15 minutes) before breakfast and at night (one [8 mg × 1] capsule dosed between 8 PM and midnight and no sooner than 1 hour after dinner), or to ORMD-0801 16 mg QD (two [8 mg × 2] capsules) dosed at night (between 8 PM to midnight and no sooner than 1 hour after dinner), or to matching placebo.

In order to maintain the blind, a double dummy design will be used. All subjects will receive 1 capsule in the morning (1 × 8 mg ORMD-0801 or 1 matching placebo capsule) and 2 capsules at

night (2 × 8 mg ORMD-0801 or 1 matching placebo capsule). The IWRS will be used for the creation, maintenance, and communication of the randomization scheme for the trial. The Investigational Site pharmacist or designee will follow this randomization schedule to dispense the appropriate study treatment.

5.3 Study Treatment Administration

Subjects will be randomized (Visit 1) to 26 weeks of double-blind treatment to one of the following four treatment arms from Week 0 (Visit 1) to Week 26 (Visit 6):

1. ORMD-0801 8 mg once-daily at night – QD: 1 x 8 mg capsule between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 2 matching placebo capsules (1 in the morning and 1 at night).
2. ORMD-0801 8 mg twice daily – BID: 1 x 8 mg capsule each morning approximately 45 minutes (±15 minutes) prior to breakfast and 1 x 8 mg capsule each night prior to bedtime (between 8 PM to 12 Midnight and no sooner than 1 hour after dinner) and 1 matching placebo capsule at night.
3. ORMD-0801 16 mg once-daily at night – QD: 2 x 8 mg capsules between 8 PM to 12 Midnight and no sooner than 1 hour after dinner and 1 matching placebo capsule in the morning.
4. Matching placebo.

5.4 Measuring Subject Compliance

Dosing compliance will be assessed through a count of unused study medication at Visits 2-6 and ET Visit (if applicable) (refer to Table 2).

5.5 Drug Accountability

In accordance with current GCP, the Investigational Site will account for all study treatment supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the Investigational Drug accountability record according to the SOP of the Investigational Site. Copies of the Investigational Drug accountability record will be provided to the Sponsor.

Study treatment will only be dispensed to subjects enrolled in this protocol and only as directed by this protocol. Administration of study treatment will be accurately recorded in each subject's source documents and eCRF.

5.6 Concomitant Medications and Supplements

All medications and supplements (other than study treatment) taken by the subject from Visit 1 through the Follow-up Visit will be considered "concomitant" medications and supplements. Medications and supplements taken prior to Visit 1, which are no longer being taken at the time of Visit 1 will be considered "prior" medications and supplements.

All medications and supplements taken within 30 days prior to the first dose of study treatment and concomitant medications and supplements taken during the study will be recorded in the subject's source documentation and in the eCRF.

If a subject requires the use of any of the prohibited medications and supplements listed below, the Investigator will contact the Sponsor and the Medical Monitor to discuss the subject's continued participation in the study. In the event of an emergency, subjects will be treated at the discretion of the Investigator according to acceptable community standards of medical care.

The following are prohibited medications:

1. Any Investigational Drug other than ORMD-0801 (or placebo) within 30 days prior to Visit 1 through the Follow-up Visit.
2. Treatment involving injected insulin unless required for rescue.
3. Thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to Screening.
4. Use of oral, intravenous, or intramuscular steroids for one month prior to enrollment. Intra-articular and/or topical corticosteroids are not considered systemic.
5. Medications known to modify glucose metabolism or decrease the ability to recover from hypoglycemia such as oral, parenteral, and immunosuppressive or immunomodulating agents. Inhaled nasal steroids are permissible.
6. Weight loss preparations either approved and marketed or used in OTC preparations except for GLP-1 used in the treatment of underlying diabetes.

If the subject initiates prohibited drug therapy, or if the Investigator determines that use of a prohibited therapy is in the best interest of the subject's health and well-being, the Investigator and the Sponsor will jointly decide to continue or discontinue study treatment for the subject.

Medications and supplements should be recorded according to the generic name when possible. The use of concomitant medications and supplements should be limited to those that are medically necessary. Any medication or supplement used should have an indication recorded. For concomitant medications and supplements, this indication must be represented as either for the treatment of an AE, the management of a pre-existing condition, or for prophylaxis.

Dosage increases for any concomitant medication or supplement should be noted and the reason for the dosage increase recorded as an AE (assumes worsening condition). The side effects of concomitant medications will be recorded as AEs.

Any subject whose condition becomes disqualifying during the study may be treated for that condition. If the condition is suspected during Screening, the subject should not be enrolled. Treatment of the condition should be instituted according to the Investigator's/attending physician's judgment.

Medications that have no treatment intent but rather are part of supportive routine care such as local anesthetics, intravenous solutions to maintain fluid balance and keep access open, medications used for prophylaxis, and narcotics for postsurgical pain must also be recorded in the subject's medical record and eCRF.

5.7 Dietary Restrictions

Subjects will be required to fast overnight for 10 hours prior to Screen 1 and prior to all study visits except for the CGM application visits (Screen 2 and Visit 5).

Excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) will not be allowed from Screening through the Follow-up Visit. Excessive alcohol use or binge drinking will be discouraged during the study, and alcohol will be prohibited 72 hours prior to each visit. Subjects should not use any recreational or illicit drugs within one year prior to Screening through Follow-up Visit. No cannabinoid products will be allowed during the 1 week prior to each visit.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 Safety Assessments

6.1.1 Weight and Height

Height and weight will be measured as indicated in Table 2. The subject will be clothed while being weighed, but should remove shoes, coats, jewelry, and other accessories. Height will be measured with the subject wearing no shoes at Screen 1 only.

6.1.2 Vital Signs

Vital signs (including seated SBP/DBP and heart rate) will be recorded at all visits as described in Table 2. Vital signs will be measured after the subject has been sitting for at least 5 minutes in a quiet environment and prior to any blood draw that occurs at the same time point. The recorded seated SBP/DBP value will be the mean of two measurements taken 2 minutes apart and always using the non-dominant arm.

6.1.3 Physical Examination

A physical examination will be performed as described in Table 2 (Screen 1, Visits 1, 6, 7, and ET). The physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological examination.

6.1.4 12-Lead ECG

A 12-lead ECG will be performed as indicated in Table 2 (Screen 1, Visits 6, 7, and ET). The 12-lead ECG will be recorded after the subject has been resting at least 5 minutes in the supine position in a quiet environment. ECGs will be read for QT and QTc (Fridericia's) intervals, and clinically significant abnormalities. The Principal Investigator will review all ECG results and initial and date a copy for storage in the source document.

6.1.5 Clinical Laboratory Tests

Blood and urine for clinical laboratory assessments will be collected and processed using standard procedures as indicated in Table 2 (Screen 1, Visits 1, 3, 6, 7, and ET). All clinical laboratory tests will be performed by the Central Laboratory.

The Principal Investigator will review all laboratory results and initial and date a copy for storage in the source document. A clinically significant abnormal lab test will be reported as an AE. In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether the abnormality is clinically significant.

6.1.5.1 Clinical Labs

The clinical labs will include the following hematology, serum chemistry, urinalysis, and serum lipid panel tests:

Hematology

- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- Red blood cell distribution width
- Red blood cell count
- White blood cell count with differential
- Reticulocyte count

Serum Chemistry

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)

- Gamma-glutamyl transferase (GGT)
- Total bilirubin
- Alkaline phosphatase
- Albumin
- Total Protein
- Blood urea nitrogen (BUN)
- Creatinine
- Uric acid
- Glucose
- Calcium
- Phosphorus
- Total cholesterol
- Triglycerides
- High-density lipoprotein cholesterol (HDLC)
- Low-density lipoprotein cholesterol (LDLC)
- A1C
- C-peptide
- CRP (C-Reactive Protein)
- TSH

Urinalysis

- Appearance (color and character)
- Bilirubin
- Urobilinogen
- Protein
- Glucose
- Ketones
- Leukocyte esterase
- Urine blood
- Nitrite
- pH
- Specific gravity

6.1.5.2 Pregnancy Test

For women of childbearing potential (WCBP) only: Serum hCG test will be performed at Screen 1 and urine pregnancy test will be performed on Visits 1, 3, 6, 7, and ET (if applicable); for women that are not of childbearing potential: Serum FSH test will be performed at Screen 1 only (refer to Table 2).

6.1.5.3 Serology

Serology tests (Hepatitis B, C, and HIV) will be performed at Screen 1 (Table 2).

6.1.5.4 Additional Bloodwork

In addition to the blood tests listed above, A1C, C-peptide, CRP (C-Reactive Protein), and TSH will be performed as a part of serum chemistry labs, and samples for FPG will be collected as indicated in Table 2.

6.1.5.5 Urine Drug Screen

Urine drug screen will be completed at Screen 1 (Table 2), according to the laboratory manual provided by the Central Laboratory. These will include testing for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, and opiates. Occasional intermittent use of cannabinoid products will be allowed provided that no cannabinoid products have been used during the 1-week prior to each visit and until the end of the study.

6.2 Efficacy Assessments

6.2.1 Hemoglobin A1c (A1C)

Mean and mean changes from baseline over time for A1C will be collected at visits indicated in Table 2.

6.2.2 Fasting Plasma Glucose (FPG)

Mean and mean changes from baseline over time for FPG will be collected at visits indicated in Table 2.

6.2.3 Continuous Glucose Monitoring (CGM)

CGM Dexcom G7 devices will be provided at Screen 2 and Visit 5. Each visit requiring CGM application will occur 10 days prior to the CGM removal visits (Visits 1 and 6 within ± 1-day window) (Table 2). Data will be collected for 10 days.

6.2.4 C-peptide Measurement

Means and mean changes from baseline over time for C-peptide will be collected at visits indicated in Table 2.

6.2.5 Self-Monitored Blood Glucose (SMBG)

Subjects will be asked to collect daily blood glucose measurements throughout the study using the supplied glucose meter. The fasting SMBG values must be obtained at least 2-3 times a week or when subjects experience any symptoms of hypoglycemia. Subject will record information (as described in Section 6.3) in paper diaries, dispensed at visits as indicated in Table 2.

6.2.6 Fasting Insulin Monitoring

Fasting blood insulin will be used to determine HOMA estimate at visits indicated in Table 2.

6.3 Paper Diary

Paper diaries will be dispensed and collected at each visit (refer to Table 2). Subjects will be trained to enter specific data into the diary and data will be reviewed for completeness of entries.

The following information will be recorded:

- Fasting SMBG values at least 2-3 times a week.
- Hypoglycemic Events: exact time and date of occurrence; symptoms experienced and interventions, if any, such as administration of rescue medication; and specific circumstances.

The Principal Investigator or designee will review the diary data and provide advice on glucose control if necessary.

7 ADVERSE EVENTS AND SAFETY REPORTING

7.1 Safety and Tolerability Assessments

Safety and tolerability will be assessed on an ongoing basis by review of reported AEs, physical examinations, 12-Lead ECGs, weight, vital signs (SBP/DBP and heart rate), prior and concomitant medications and supplements, and clinical labs (hematology, serum chemistry, urinalysis, and serum lipid panel).

7.2 Definition of Adverse Event

An adverse event (AE) is defined in 21 CFR 312.32(a) as follows:

> Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease during the study and does not imply any judgment about causality.

Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first randomized dose of study treatment (active or placebo).

7.3 Adverse Events of Special Interest

7.3.1 Adverse Events of Hypoglycemia

Episodes consistent with hypoglycemia will be reported as adverse events of special interest. They will be collected from the patient diaries issued to patients. Due to the specific relevance of hypoglycemia as a limiting factor with injectable insulin therapy, AEs of hypoglycemia will therefore be reviewed at every visit. All hypoglycemic events will be reported on a special hypoglycemia AE eCRF page. This report will include the following information:

- Subject symptoms.
- Type of symptoms.
- BG value during the hypoglycemic event and the event severity based on Common Terminology Criteria for Adverse Events (CTCAE) criteria.
- Whether treatment was required.
- Whether assistance was required for treatment.
- What specific treatment, if any, was used.

Based on the Investigator's discretion, only symptomatic hypoglycemic events will be reported on the AE page. Instructions will be given to sites to additionally report episodes consistent with hypoglycemia requiring third party assistance as Serious Adverse Events (SAE).

Collection of data from the hypoglycemia AE eCRF including episodes consistent with hypoglycemia will allow analysis and characterization of hypoglycemia according to accepted ADA definitions (Seaquist et al, 2013) and according to common cut-off values. Analysis of the number of hypoglycemic events, percentage of subjects having at least one hypoglycemic event and average duration of hypoglycemic events will be performed using cutoffs of BG < 54 mg/dL and BG < 70 mg/dL.

7.4 Adverse Events of Hyperglycemia

Hyperglycemia is the result of inadequate treatment and a pre-condition for enrolment into the study. Therefore, in general, hyperglycemia is not considered an AE. However, hyperglycemia may occur in participants during the study either due to worsening diabetes or lack of efficacy of study medication. For standardization purposes, hyperglycemia is defined as a blood glucose reading > 300 mg/dL regardless of symptoms. Subjects who have a blood glucose reading > 300 mg/dL will have the reading repeated 1-2 hours later. If a subject's glucose remains above 300 mg/dL or for persistent symptoms of hyperglycemia, the subject will be instructed to contact the Investigational Site for Follow-up. Based on the Investigator's discretion, only symptomatic hyperglycemic events will be reported on the AE page. Protocol specified algorithms will allow subjects to receive additional rescue medication that may enable them to remain in the study (Section 3.5).

7.5 Definition of Serious Adverse Event

A SAE is defined in 21 CFR 312.32(a) as follows:

> An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
>
> - Death.
> - Life-threatening AE.
> - Inpatient hospitalization or prolongation of existing hospitalization.
> - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
> - Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject, or the subject requires medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

An AE is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

7.6 Eliciting and Reporting of Adverse Events

AE monitoring will start immediately following the first dose at Visit 1 and will continue through the Follow-up Visit. Any subject with a possible study treatment-related AE at the Follow-up Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether related or unrelated to study treatment that occurs within 30 days following the last dose of study treatment will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded in the subject's source documentation and in the eCRF.

Subjects will be instructed to report all AEs experienced during the study, and subjects will be assessed in clinic for the occurrence of AEs throughout the study. To avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs, including pretreatment and TEAEs, reported by the subject, observed, or otherwise identified by the Investigator or other Investigational Site personnel will be documented.

Medical conditions existing at Screening should be recorded as medical history. New or worsening pre-existing medical conditions or diseases are considered AEs if they arise or worsen after the Randomization Visit and should be recorded as AEs.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE if it occurs or is detected following the first dose of study treatment at Visit 1 through the Follow-up Visit. Conditions leading to planned surgical procedures are not AEs if the condition(s) was (were) known before study treatment. In the latter case, the condition should be reported as medical history.

7.6.1 Routine Reporting of Adverse Events

All AEs, whether or not associated with study treatment, that are observed by the Investigator, other Investigational Site personnel, or the subject will be recorded in the subject's source documentation and on the AE page of the eCRF. Copies of the SAE eCRF pages or an SAE listing generated based on the eCRF pages will be submitted to the Sponsor at regularly scheduled intervals to allow the Sponsor to meet expedited regulatory reporting requirements under 21 CFR 312.32 (see Section 7.6.2 for further detail) and regular regulatory reporting requirements under 21 CFR 312.33.

For each AE, the following information will be entered in the eCRF:

- Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event).
- Date of onset of any new AE or worsening of a previously observed AE.
- Date of resolution of the event (or confirmation ongoing).
- Whether the event is serious (per definition in Section 7.5), and if so, the reason it is considered serious.
- Severity of AE (per definition in Section 7.8).
- Assessment of the causality of the AE to the study treatment (per definition in Section 7.7).
- Action taken in treating the AE (including concomitant medications or therapies administered) and/or change in the study treatment administration or dose (including whether the study treatment was temporarily interrupted or discontinued).
- Outcome of AE (per definition in Section 7.10).

7.6.2 Reporting of Serious Adverse Events, Including Death

The Sponsor will adhere to all expedited regulatory reporting requirements as per 21 CFR 312.32.

If an SAE, including death occurs during this study or within 30 days following the last dose of the study treatment, the Investigator must notify the Medical Monitor **within 24 hours** after becoming aware of the event.

Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE Form within the time frames outlined in the protocol. This timeframe also applies to additional new information (Follow-up) on previously forwarded SAE reports.

Medical Monitor:

Name
Title
Office:
Cellular:
Email:

SAE Forms will be provided by the Sponsor or Sponsor designated contract research organization (CRO). If all information is not known at the time of initial reporting, an initial report should still be made. In the event there is a question as to whether the experience is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. For all SAEs, the Investigator must pursue and provide information to the study Medical Monitor in accordance with the timeframes for reporting specified above. In general, this will include a description of the AE in enough detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the Medical Monitor.

In the event of a medical emergency or an SAE that is unexpected (as defined in Section 7.9) and possibly related to the study treatment(s) (i.e., an adverse reaction or suspected adverse reaction as defined in Section 7.7), the Investigator in consultation with the Medical Monitor may request that a blind be broken in instances when the knowledge of the assigned treatment may impact the subjects' medical management.

The initial SAE Form and any subsequent follow-up SAE Forms submitted to provide more accurate, corrected, or new information must be signed by the Investigator. The Investigator and Investigational Site Personnel must make every reasonable effort to obtain from other institutions, if necessary, all supporting medical case records as needed to comply with expedited Investigational New Drug application (IND) safety reporting requirements.

If the SAE involves expedited IND safety reporting (as determined by the Sponsor or designee), all supporting medical records must be submitted to the Sponsor or designee within 4 calendar days for death or life-threatening events, and 10 calendar days for all other events. In cases where medical records and supporting documentation are unobtainable, the Investigator must generate a narrative of the event utilizing, when necessary, interviews with the subject, their family members and care givers as appropriate.

The Investigator must also promptly inform the governing IRB of the SAE in accordance with the governing IRB's requirements. Any SAE that is determined by the Sponsor to be reportable to the FDA as an IND Safety Report (as defined in 21 CFR 312.32) will be reported to FDA by the Sponsor or designee within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his/her IRB. Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor or designee within the specified time frames and will be provided to the Investigator for submission to his/her IRB.

The Investigator, Medical Monitor, and Sponsor will review each SAE report and evaluate the relationship of the adverse experience to study treatment and underlying disease. Based on this assessment, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical trial. If the discovery of a new adverse experience related to the study treatment raises concern over the safety of continued administration of study treatment, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol.
2. Discontinuation or suspension of the study.
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings.
4. Modification of previously identified expected adverse experiences, to include adverse experiences newly identified as study treatment related.
5. A MedWatch form will be used to create a patient summary narrative for all SAEs expected or unsuspected.

7.6.2.1 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study medication, the Investigator should report the pregnancy to CRO within 24 hours of being notified. Safety personnel will then forward the Exposure In-Utero form to the Investigator for completion.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

7.7 Causality Assessment of Adverse Events

For all AEs, the Principal Investigator will provide an assessment of causal relationship to the study treatment (active or placebo). The causality assessment must be recorded in the subject's source documents and on the AE eCRF. Causal relationship will be classified according to the following criteria:

1. *Unrelated*: The event is clearly due to causes other than the active study drug.
2. *Unlikely*: The event is doubtfully related to active study drug. The event was most likely related to other factors, such as the subject's clinical state, concomitant drugs or other therapeutic interventions.
3. *Possible*: The event follows a reasonable temporal sequence from the time of active study drug administration but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs.
4. *Probable*: The event follows a reasonable temporal sequence from the time of active study drug administration and follows a known response pattern to the drug. The toxicity cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs.
5. *Definite*: The event follows a reasonable temporal sequence from the time of active study drug administration; follows a known response pattern to the drug; cannot be reasonably explained by other factors, such as the subject's condition, concomitant drugs or therapeutic interventions; AND either occurs immediately following active study drug administration, improves on stopping the study drug, or reappears on re-exposure.

7.7.1 Potential Adverse Events Associated with ORMD-0801

Hypoglycemia and associated symptoms (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), have been associated with insulin administration, including ORMD-0801. Animal reproductive studies have not been conducted with ORMD-0801. It is not known whether ORMD-0801 can cause fetal harm when administered to a pregnant woman. It is also not known whether this product is excreted in human milk. Pregnant or breastfeeding women are excluded from this study.

Long-term animal studies have not been completed to assess whether ORMD-0801 impairs fertility.

7.8 Adverse Event Severity Assessment

The severity of each AE will be graded according to the NCI CTCAE, version 5. The severity of AEs that are not specifically listed in the CTCAE will be categorized according to the general guidelines provided in the CTCAE, and as summarized in the table below.

Table 3. General Guidelines for Severity Assessment of Adverse Events

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.].
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden].
Grade 4: Life-threatening consequences; urgent intervention indicated.
Grade 5: Death related to AE.

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above in Section 7.5.

7.9 Expectedness of Adverse Event

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

> An AE is considered "unexpected" if it is not listed in the IB or at the specificity or severity that has been observed; or, if an IB is not required or available, the AE is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.10 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to International Council for Harmonisation (ICH) Topic E2B, ICH Guideline.

- **Recovered/Resolved:** The subject has recovered fully from the AE without any remaining effects or impairment.
- **Recovered/Resolved with Sequelae**: The subject has recovered, but with an after effect possibly due to disease or treatment.
- **Not Recovered/Not Resolved:** The condition is still present.
- **Fatal:** Fatal should only be used when death is possibly related to the AE.
- **Unknown**: The primary outcome is not known at the time of the final assessment. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed

until an outcome is known or followed up to the Final Study Visit. Any subject with a possible study treatment-related AE at the Final Study Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether related or unrelated to study treatment (active or placebo), that occurs within 30 days following the last dose of study treatment will be followed until resolution or stabilization of the event.

7.11 Clinical Findings

Any significant clinical findings at the Follow-up Visit will be followed until the condition returns to pre-study status, stabilizes, or can be explained as not being study treatment related. If the clinical finding is reported as an AE (per the criteria outlined in Section 7.6), the Follow-up procedures for AEs defined above will apply.

8 STATISTICAL METHODS

This section describes the statistical methods to be used for the analysis and reporting of data collected under Protocol No. ORA-D-013-3. Additional details will be provided in the statistical analysis plan.

8.1 Power and Sample Size

The primary efficacy endpoint is the change from baseline in A1C at Week 26 (Visit 6). Based on subgroup results from a previous study, a drop in A1C of 0.6% is expected with a standard deviation of 1.1. Having 75 subjects per treatment group will ensure that the power will be at least 90% (with an alpha = 0.05). Assuming an approximate 10% drop out rate, 75 randomized subjects per treatment group would yield approximately 67 completers per treatment group.

8.2 Analysis Sets

The Safety Population will comprise all randomized patients who receive at least one dose of study medication. This population will be used for all summaries of patient accountability, demographic and baseline data, and safety information, including adverse event incidence and laboratory data.

The Full Analysis Set (FAS) will consist of all randomized patients. This population will serve as the basis for all efficacy analyses.

A Per Protocol Set (PPS) will consist of patients in the FAS who satisfy all enrollment criteria and are protocol compliant. Patients' data collected after the start of rescue medication will be excluded from the Per Protocol analyses. Criteria for excluding patients from the PPS will be finalized before unblinding the database.

8.3 Primary Efficacy Evaluation

The primary endpoint for this study is the change from baseline (Visit 1) in A1C at 26 weeks (Visit 6) for the active and placebo groups. Randomization will occur at Visit 1 (Week 0), where subjects

will be stratified by Screening A1C values (A1C < 9.0 and A1C ≥ 9.0) and site (each site will be stratified independently). To preserve alpha, a hierarchical testing strategy will be used. The order of testing for active therapy versus placebo is: 1) ORMD-0801 16 mg once-daily, 2) ORMD-0801 8 mg twice daily and 3) ORMD-0801 8 mg once-daily.

Change from baseline in A1C at 26 weeks will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment and site as categorical fixed effects and baseline A1C as a covariate. The treatment policy estimand is the primary estimand and will be estimated based on the FAS using Week 26 measurements. The primary statistical analysis will be a pattern mixed model using multiple imputation (MI) to handle missing data assuming that the missing data mechanism is missing at random (MAR) within the groups used for imputation.

Intermittent missing data in an endpoint for subjects who complete treatment will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. This imputation will be done by the treatment group, using the MI procedure in SAS 9.4. The variables to be used in the imputation are treatment, corresponding baseline values and values observed at all double-blind visits.

Missing data in an endpoint for subjects who prematurely discontinue treatment will be imputed from the observed data collected from subjects in the same treatment arm who prematurely discontinue treatment (retrieved dropouts). Intermittent missing data will be imputed using the Markov Chain Monte Carlo (MCMC) methodology. Once the data follows a monotone missing pattern, the monotone regression method will be used. If there are insufficient retrieved dropouts, the washout method will be used in which missing data in an endpoint from both treatment arms will be imputed using observed endpoint data from the placebo arm. When imputing missing values in the treatment arm, no intermediate endpoint values will be used, so only baseline data, baseline A1C and other covariates will be included in the model. When imputing missing values in the placebo arm, baseline data, intermediate endpoint values, and baseline A1C and other covariates will be included in the model. This imputation will be done using the MI procedure in SAS 9.4.

The steps for conducting the primary analysis using the imputed datasets are:

Step 1: Impute missing data as described above using PROC MI to form M complete datasets. M can vary and will be described in more detail in the Statistical Analysis Plan.

Step 2: Analyze the change from baseline to Week 26 in A1C using an Analysis of Covariance (ANCOVA) model with treatment and site as categorical fixed effects and baseline A1C as a covariate for each of the M complete datasets.

Step 3: Combine the results from each of the M complete datasets using Rubin's rule as implemented in PROC MIANALYZE in SAS 9.4.

8.4 Secondary Efficacy Evaluation

The incidence of A1C < 7% at 26 weeks will be analyzed as a binary endpoint using a g-computation estimator with site and baseline A1C as covariates. The steps involved in this g-computation estimator are:

1. Fit 3 logistic models (one for each of the active treatment groups) with maximum likelihood that regresses the outcome of the active treatment group and placebo with prespecified baseline covariates (site and baseline A1C). Each of the 3 logistic models will only include subjects randomized to that specific active treatment and placebo. The model will include an intercept term.

2. For each of the active treatment groups, the following steps will be performed:

    a. For each subject, regardless of treatment group assignment, compute the model-based prediction of the probability of response under treatment using the subject's specific covariates.

    b. Estimate the average response under treatment by averaging (across all subjects in the trial) the probabilities estimated in Step 2.

    c. For each subject, regardless of treatment group assignment, compute the model-based prediction of the probability of response under control using the subject's specific baseline covariates.

    d. Estimate the average response under control by averaging (across all subjects in the trial) the probabilities estimated in Step 4.

    e. The estimates of average response rates in the two treatment groups from Steps 3 and 5 will be used to estimate the odds ratio.

The multiple imputation datasets used in the primary A1C analysis will be used to derive the incidence of A1C < 7%.

Change from baseline in fasting plasma glucose at 26 weeks will be analyzed as a continuous variable in a manner consistent with the primary endpoint with the associated baseline response as a covariate in addition to baseline A1C.

In order to maintain an overall Type I error rate of 0.05 a hierarchical approach will be used. The secondary endpoints will be tested in the following order:

- Incidence of A1C < 7% at 26 weeks, and
- Change from baseline in fasting plasma glucose at 26 weeks.

8.5 Exploratory Efficacy Evaluation

The exploratory efficacy endpoints will be evaluated for:

- The primary estimand based on FAS using the Week 26 data regardless of adherence to randomized treatment and initiation of rescue medication.

- The secondary estimand based on FAS using the Week 26 data censored after the start of rescue medication.

Each of the Week 26 continuous efficacy endpoints will be analyzed as a continuous variable in a manner consistent with the primary endpoint with the associated baseline response as a covariate in addition to baseline A1C.

Each of the Week 26 binary efficacy endpoints will be analyzed as a binary variable in a manner consistent with secondary efficacy binary endpoint.

8.6 Sensitivity Analysis

The primary analyses for assessing change in A1C are valid if the missing data are missing at random (MAR), meaning that the probability of a value being missing, conditional on the observed data and factors in the statistical model, is random and not dependent on the unknown value of the missing data point. Therefore, a sensitivity analysis under missingness not at random (MNAR) will be conducted for change from baseline at Week 26 in A1C to evaluate the robustness of efficacy results and the effect of missing data.

A sensitivity analysis using the missing not at random (MNAR) option in SAS 9.4 PROC MI will be performed. In this sensitivity analysis, intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. This imputation will be done by the treatment group, using the MI procedure in SAS 9.4. The variables to be used in the imputation are treatment, baseline A1C and values observed at all double-blind visits. Then all the monotone missing values will be multiply-imputed using the imputation model built from the control group (i.e., assuming the missing data in the treatment group will have a profile that equals the profile of the control group for all time points). The missing data imputation will be implemented using PROC MI in SAS 9.4 with the MNAR statement. Once the completed data sets are formed, the same ANCOVA analysis model as specified for the primary analysis will be applied to each completed set and the inference drawn using Rubin’s combination rules (SAS PROC MIANALYZE). While the results will be combined using SAS PROC MIANALYZE, it is known that this approach may produce an inflated variance estimate for the treatment comparison. To get a correct variance, a pattern mixture model approximation method will also be used. Results from both the MIANALYZE and the pattern mixture model approximation will be presented as sensitivity analyses.

As additional sensitivity analysis using the tipping-point approach will be conducted to assess the robustness of the primary analysis approach. Each of the active treatment groups will be compared to placebo independently.

If it is plausible that, for each of the active treatment groups, the distribution of missing primary endpoint responses has a smaller expected reduction than that of the corresponding distribution of the observed primary endpoint responses, the conclusion under the MAR assumption should be examined. It is desired to impose a fixed and definite set of quantities to encapsulate the change in efficacy associated with withdrawal (missing) for the active treatment group, and the tipping point multiple imputation analysis as described in Ratitch et al. (2013) will be applied.

Tipping point analysis is a means of exploring the influence of missingness on the overall conclusion from statistical inference by positing a wide spectrum of assumptions regarding the missingness mechanism (from less conservative to more conservative). The analysis finds a (tipping) point in this spectrum of assumptions, at which conclusions change from being favorable to the experimental treatment to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying the tipping point. The tipping point can be identified while the result is no longer statistically significant. This imputation analysis will use a specified sequence of shift parameters, which adjusts the imputed values for observations in the active and placebo treatment groups.

For each of the active treatment groups, a two-dimensional matrix will be created exploring various decreases in effectiveness for missing data in the active treatment group and various increases in effectiveness for the missing data in the placebo group to determine the tipping points at which statistical significance is no longer obtained. For example:

- An active treatment group could have an average change from baseline in A1C values for the missing data of -0.600, -0.575, -0.550, -0.525, -0.500, -0.475, -0.450, -0.425 and -0.400 (decreasing levels of effectiveness) (assuming the active treatment group shows an overall average decrease of 0.600 in change from baseline for A1C)

- The placebo treatment could have an average change from baseline in A1C values for the missing data of 0.000, -0.025, -0.050, -0.075, -0.100, -0.125, -0.150, -0.175 and -0.200 (increasing levels of effectiveness) (assuming the placebo treatment group shows an overall change of 0 in change from baseline for A1C)

- This example would create a 9x9 two-dimensional matrix of p-values from which to examine the underlying tipping points for the indicated active treatment group. Each active treatment group would have its own two-dimensional matrix.

8.7 Examination of Subgroups

Analysis for the primary and secondary endpoints will be provided for the following subgroups of baseline factors:

- Sex (Male, Female)
- Age Group (60 years and younger, over 60 years)
- Baseline A1C (Less than or equal to 9.0, Greater than 9.0)
- Race
- Ethnicity

For each subgroup, the similar ANCOVA model as the primary and secondary analyses will be performed by subgroup variable. Descriptive summary statistics including mean, SD, 95% Confidence Intervals and median will also be provided. Subsequently, subgroups may be identified on a data-driven basis, and such analyses will be considered exploratory and hypothesis generating only.

8.8 Other Statistical Efficacy Considerations

The latest available measurement, at or prior to the randomization visit, will be used as the baseline measurement. If no measurement(s) have been obtained, at or prior to randomization, the baseline value will be left missing.

8.9 Secondary Safety Evaluation

Change in hypoglycemia rates from baseline during the Double-Blind Treatment Period, and the Follow-up Visit will be provided using descriptive statistics (i.e., mean, median, range, and standard deviation). This analysis will use completed subjects (as predicting hypoglycemia rates could lead to an undercounting of events and a misinterpretation of the data).

All AEs will be coded by Preferred Term using the MedDRA classification dictionary. The incidence of TEAEs will be summarized by treatment group, and by severity and relationship to study drug. Serious AEs (SAEs) and AEs leading to withdrawal from the study will be tabulated.

8.10 Safety Evaluation

Other safety will be evaluated on the basis of vital signs, physical examinations, clinical laboratory assessments, prior and concomitant medications and supplements, and ECG findings. Changes from baseline in vital signs, physical examinations, weight, clinical laboratory values, and ECGs will be summarized by treatment group using descriptive statistics.

8.10.1 Safety Population

All randomized subjects who receive at least one dose of study treatment will be included in the safety analysis population.

Adverse events will be described as "Emergent," defined as any AE that started (or worsened) after receiving the first dose of randomized treatment.

8.10.2 Hypoglycemia Rates

Change in hypoglycemia rates from baseline during the Double-Blind Treatment Period and the Follow-up Visit will be provided using descriptive statistics (i.e., mean, median, range, and standard deviation). This analysis will use completed subjects (as predicting hypoglycemia rates could lead to an undercounting of events and a misinterpretation of the data).

8.10.3 Adverse Events

AEs will be coded using the most current version of MedDRA at the time of study startup. The severity of AEs will be graded according to NCI CTCAE version 5. AEs will be regarded as "pretreatment" if they occur prior to Visit 1. Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first dose of IP on Visit 1.

The incidence of TEAEs will be tabulated by MedDRA preferred term, system organ class, treatment group, severity, and assigned relationship to study treatment. The incidence for each TEAE will be provided as the total number of subjects that experienced the TEAE, as well as the percentage of the population that this number represents. If a TEAE is reported more than once for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

TEAEs will be listed for individual subjects, along with information regarding onset and end dates, onset time where available, severity, seriousness, relationship to study treatment, action taken, and outcome. A similar listing will be prepared for the pretreatment AEs.

Pretreatment AEs and TEAEs that lead to withdrawal from the study will be separately listed and summarized. Similarly, separate tabulations and listings will be prepared for pretreatment and treatment emergent SAEs.

Descriptive statistics will be generated as appropriate (i.e., frequency for categorical data). Inferential statistical analysis comparing the AE data between active and placebo is not planned.

8.10.4 Laboratory Evaluations

Individual clinical lab (hematology, serum chemistry, urinalysis, and serum lipid panel) values will be listed by visit and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Individual change from baseline (Visit 1) in laboratory values will be calculated and summarized

descriptively. Shift tables from baseline (Visit 1) to the end of the 26-week Double-Blind Treatment Period (Visit 6, Week 26) will also be produced for the laboratory assessments based on the categories of low, normal, and high. A clinically significant change from baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.10.5 Vital Signs

Individual vital sign measurements (height, weight, seated SBP/DBP, and heart rate) will be listed by measurement time and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation). Individual change from baseline (Visit 1) in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from baseline will be recorded as a TEAE if deemed appropriate by the Investigator.

8.10.6 12-lead ECG

Individual 12-lead ECG assessments will be listed by visit and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data).

8.10.7 Physical Examination

Individual physical examination findings will be listed by visit. A clinically significant change from baseline (Visit 1, Week 0) will be recorded as an AE if deemed appropriate by the Investigator.

8.10.8 Prior and Concomitant Medications and Supplements

Medications and supplements will be coded using the most current version of the WHO Drug Reference List at time of study startup, which employs the Anatomical Therapeutic Chemical classification system.

Concomitant medications and supplements will be listed for individual subjects. A similar listing will be prepared for prior medications and supplements taken within 30 days prior to the first dose of study treatment. The incidence of these prior and concomitant medications and supplements will be summarized.

9 DATA MANAGEMENT

9.1 Data Collection

All data required by the study protocol will be collected in a validated database according to the CRO's SOPs.

9.1.1 Electronic Data Capture

Data from the source documents will be entered into the EDC system by authorized Investigational Site personnel. Data Management staff, using both electronic and manual checks, will systematically check the data. Errors or omissions will result in queries (that can be issued by the Study Monitor or Data Management staff), which will be presented to the Investigational Site within the EDC system. The Investigational Site will resolve the queries within the EDC system. The Study Monitor and Data Management staff will review the responses as part of the query resolution process. The EDC system will track the queries with the corresponding responses.

Medications and supplements entered into the database will be coded in the EDC system using the most current version of the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. AEs and medical history will be coded in the EDC system using MedDRA terminology.

Laboratory samples will be processed by the Central Laboratory. Results will be reported to CRO and imported into the database.

9.2 Quality Assurance and Database Lock

A 100% critical variable review of all key safety and secondary endpoint data in the database will be performed. Following this review, a data quality control audit equal to the $\sqrt{N} + 1$ (N being the number of subjects entered in the database), will be performed.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Sponsor, the Investigator, CRO, and the study biostatistician.

10 AMENDMENTS/MODIFICATIONS OF THIS PROTOCOL

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. As the study progresses it may become necessary to change or modify parts of the protocol. The Sponsor or designee is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible

for submitting protocol amendments to the appropriate IRB. Approval by the IRB must be obtained before changes are implemented.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the study. The eCRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB will be notified in writing of such departure from protocol.

11 INVESTIGATOR OBLIGATIONS

11.1 Regulatory Documentation

Before the trial starts, Essential Documents, as defined in ICH E6 will be generated and placed in both the Investigator's and Sponsor's files. Additional Essential Documents will be added to both files as new information becomes available and at the completion or termination of the trial as defined in ICH E6.

11.2 Protection of Human Subjects

11.2.1 Declaration of Helsinki

The Investigator will conduct this study in accordance with the Declaration of Helsinki (1964), including all amendments up to and including the October 2013 revision.

11.2.2 Good Clinical Practice and Regulatory Compliance

The Investigator will conduct this study in accordance with the principles of GCP (current ICH guidelines) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The study will be conducted as described in the approved protocol, with amendments and in accordance with the obligations of clinical Investigators set forth in Form FDA 1572 and in 21 CFR 50, 54, 56, and 312.

11.2.3 Institutional Review Board

The Investigator is responsible for the submission of the protocol, ICF, and other written materials (such as advertisements and diaries), along with relevant supporting data (e.g., IB), to the appropriate IRB for review and approval before the study can be initiated. The Investigator is also

responsible for submitting amendments to the protocol and ICF to the IRB for review and approval prior to implementation of the change. The Investigator is responsible for providing the Sponsor with a letter documenting the IRB approval prior to initiation of the study or implementation of the changes, respectively.

The Investigator will not have authority to implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation from the approved protocol will be documented in the source documents and eCRF.

Any deviation or change to the protocol required to eliminate an immediate hazard prior to obtaining IRB approval/favorable opinion, will be submitted as soon as possible to:

- IRB for review and approval/favorable opinion.
- The Sponsor via appropriate designees.
- Regulatory Authorities, if required by local regulations.

Documentation of IRB approval signed by the chairperson or designee of the IRB will be provided to the Sponsor via appropriate designees.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the ICF will be revised and submitted to the IRB for review and approval/favorable opinion; (2) the revised ICF will be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new ICF will be used to obtain consent from any new subjects prior to enrollment.

The Investigator is responsible for informing the IRB of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB by the Investigator.

The Investigator is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The Investigator must inform the IRB when the study is completed or terminated. After completion or termination of the study, the Investigator will submit the final clinical study report to the IRB. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

11.2.4 Subject Informed Consent

The Investigator must comply with informed consent regulations (21 CFR Part 50) and relevant state regulations (i.e., California Bill of Rights for California patients).

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and will include any additional elements required by the Investigator's institution or local regulatory authorities. The ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Investigator will obtain the IRB's written approval/favorable opinion of the written ICF. The IRB approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff, and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The ICF and any other information provided to subjects will be revised whenever important new information becomes available, which is relevant to the subject's consent, and the Investigator will obtain the IRB's written approval/favorable opinion prior to the use of the revised documents. The Investigator, or a person designated by the Investigator, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. Subjects will read and sign all revised ICFs.

11.3 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This information is detailed in the ICF provided to the subject. An agreement for the use or disclosure of any such information (PHI) will be obtained from the subject in writing (HIPAA authorization) prior to performing any study-related procedures. Disclosure of subject medical information obtained as a result of this study to third parties other than those noted below is prohibited.

Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated because of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study treatment and therefore, may be disclosed by the Sponsor as required for disclosure as a public company to other clinical investigators, other pharmaceutical companies, the FDA, and other government agencies. All reports and communications relating to subjects in this study will identify each subject only by their initials and subject number.

11.4 Case Report Forms

All data required by the study protocol will be recorded in the eCRF. Data from the source documents will be entered into the EDC system by authorized Investigational Site personnel. The eCRF will be updated at the time of each subject visit. Results of tests performed outside the Investigational Site will be entered as soon as available to the Investigational Site. The Principal Investigator must verify that all data entries in the eCRF are accurate and correct by signing the subject's eCRF investigator signature screen.

11.5 Source Documentation

All data entered in the eCRF must be verifiable against source documentation. Source documents may include, but are not limited to, a subject's medical record, hospital charts, clinic charts, the Principal Investigator's study files and the results of diagnostic tests.

11.6 Retention of Records

The Investigator has the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor or designee, the IRB, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time and should consist of the Essential Documents as defined in ICH E6, which include, but are not limited to, the following elements:

- Subject files, containing the completed eCRFs, supporting source documentation from the medical record (including laboratory data), and the signed ICF.
- Regulatory files, containing the protocol with all amendments and Sponsor and Investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB and Sponsor; and
- Drug accountability files, including a complete account of the receipt and disposition of the study treatment (active and placebo).

The Investigator will retain all study records for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study records for at least 2 years after the investigation is discontinued and regulatory authorities have been notified. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor will be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the Investigational Site for any or all the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

11.7 Clinical Study Report

After completion or termination of the study, a clinical study report will be prepared. The structure and content of the report will meet that described in the Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995). The Principal Investigator must verify that all information and data in the clinical study report is accurate and correct by signing the clinical study report.

12 STUDY ADMINISTRATION

12.1 Study Monitoring

This study will be monitored by the Sponsor or designee to evaluate the progress of the study; verify the accuracy and completeness of the eCRFs; assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

The Investigator will allow the Study Monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each subject in the study.

The Study Monitor will compare the eCRF data against source documentation to verify its accuracy and completeness. The Investigator and Investigational Site staff will collaborate with the Study Monitor to resolve any identified data discrepancies in a timely manner.

The Study Monitor will record any protocol deviations identified, including, but not limited to, subjects that were enrolled even though they did not meet all eligibility criteria, subjects who took concomitant medications specifically prohibited by the protocol, subjects who received the wrong study treatment or incorrect dose, and subjects who failed to comply with the protocol-defined dietary restrictions. The Investigator and Investigational Site staff will collaborate with the Study Monitor to identify the reason for each protocol deviation.

The Study Monitor will compare the Investigational Site study treatment accountability record against the study treatment inventory (unused and used) at the site. The Investigator and Investigational Site staff will collaborate with the Study Monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

12.2 On-Site Audits

The FDA, or other regulatory authorities, may request access to all study records for inspection and copying. The Principal Investigator and Investigational Site staff will cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for the purpose of conducting an inspection.

The Sponsor or designee may also request to visit the Investigational Site to conduct an audit of the study. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Principal Investigator and Investigational Site staff will cooperate with the auditors and allow access to all source documents supporting the eCRFs and other study-related documents.

12.3 Data Quality Assurance

All eCRFs must be completed by authorized Investigational Site personnel who have undergone eCRF training. Data will be entered into the eCRF as information becomes available on a visit-by-visit basis. All data recorded on the eCRFs must be supported by source documentation. The Principal Investigator must verify that all data entries in the eCRF are accurate and correct by electronically signing and dating the eCRF.

All eCRF corrections must be made by the Principal Investigator or authorized Investigational Site personnel. The Principal Investigator must authorize changes to the recorded data, and this authorization must be documented in the source documents.

Refer to Section 9 for further details regarding Data Management quality assurance, including query generation and resolution, final data review, and database lock.

12.4 Publication Policy

All information and data obtained during the study is the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical trial agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

This trial will be registered in a publicly accessible database (clinicaltrials.gov) no later than 21 days after enrollment of the first subject. Results of this trial, including negative and inconclusive, as well as positive results, will be made publicly available.

12.5 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor and CRO in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor and CRO (protocols, IBs, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor and CRO to the Investigator may not be disclosed to others without direct written authorization from the Sponsor and CRO, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

13 REFERENCES

Aly Mansour Dina et al. Genome-wide association analyses highlight etiological differences underlying newly defined subtypes of Type 2 Diabetes: Nature Genetics. 2021, 53: 1534.

Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed December 5, 2023].

Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund JY, Zinman B, Jacobson A, Sun W, Lachin JM, Nathan DM; DCCT/EDIC Research Group (2006): "The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study." Diabetes 55(12):3556-3565.

Diabetes Control and Complications Trial Research Group (1993): "The effect of intensive diabetes treatment on the development and progression of long-term complications in insulin-dependent diabetes mellitus." N Engl J Med 329(14):977-986.

ElSayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. 3. Prevention or delay of diabetes and associated comorbidities: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl. 1): S41–S48.

Li Xia et al. Validation of Swedish Diabetes Regrouping Scheme in Adult Diabetes in China: Journal of Clinical Endocrinology and Metabolism 2020, Vol. 105 (10) e3519.

Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, Zinman B (2006): "Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European A1ssociation for the Study of Diabetes." Diabetes Care 29(8):1963-1972.

Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B (2009): "Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes." Diabetes Care 32(1):193-203.

Ratitch B, O'Kelly M, Tosiello R. "Missing Data in Clinical Trials: From Clinical Assumptions to Statistical Analysis Using Pattern Mixture Models." Pharm Stat. 2013;12:337-347.

Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, and Vigersky R. (2013): "Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society." Diabetes Care, 36(5), 1384–1395.

U.K. Prospective Diabetes Study (UKPDS) Group (1998a): "Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes (UKPDS 33)." Lancet 352(9131):837-853.

U.K. Prospective Diabetes Study (UKPDS) Group (1998b): "Effect of intensive blood glucose control with metformin on complication in overweight patients with type 2 diabetes (UKPDS 34)." Lancet 352(9131):854-865.

U.S. Food and Drug Administration (2008): "Draft Guidance for Industry: Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention." U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, MD.

Xiantang Zou et al. Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. Lancet-Endocrinology and Metabolism. 2019 Vol 7 Correspondence.

Zaharia, OP et al. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study; Lancet-Endocrinology and Metabolism. 2019 Vol 7 684.