Clinical Study Protocol: ORA-D-018

Study Title:	A Randomized, Double Blind, Phase 2b Study to Evaluate the Effect of ORMD-0801 Compared to Placebo on Endogenous Glucose Production in Patients with Type 2 Diabetes Mellitus
Protocol Number:	ORA-D-018
Study Phase:	Phase 2b
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Name of Sponsor Signatory:	Miriam Kidron, PhD Chief Scientific Officer and Director Oramed Ltd.
Protocol Version:	1
Date of Version:	May 13, 2020

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned has reviewed and approved Protocol No. ORA-D-018 for issuance:

	Signature	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 of the Investigator's Brochure (IB), which was 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 of 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

SYNOPSIS

Title	A Randomized, Double Blind, Phase 2b Study to Evaluate the Effect of ORMD-0801 Compared to Placebo on Endogenous Glucose Production in Patients with Type 2 Diabetes Mellitus
Indication	Type 2 Diabetes Mellitus (T2DM)
Clinical Phase	Phase 2b
Study Treatment	ORMD-0801 (insulin)
Dose	ORMD-0801 8 mg Capsule
Dosage Regimen	BID
Formulation	Soft gel capsule [SBTI, disodium EDTA, fish oil, aerosol, and Tween 80], Recombinant Human Insulin
Mode of Administration	Oral
Primary Objective	1. To assess the differences in endogenous glucose production in subjects with type 2 diabetes treated for 4 weeks either with ORMD-0801 or matching placebo following an intravenous infusion of [6,6-$^2H_2$]-glucose tracer using AUC(0-last).
Secondary Objectives	1. To compare the change from baseline in HbA1c levels measured at Week 4 in type 2 diabetic patients treated for 4 weeks with either ORMD-0801 or matching placebo. 2. To compare the change from baseline in plasma glucose levels measured at Week 4 in type 2 diabetic patients treated for 4 weeks with either ORMD-0801 or matching placebo. 3. To compare the change from baseline in ketone levels measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 4. To compare the change from baseline in FFAs measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 5. To compare the change from baseline in TC, LDLC, HDLC, and TG measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 6. To assess the differences in endogenous glucose production in patients with type 2 diabetes treated for 4 weeks either with ORMD-0801 or matching placebo following an intravenous infusion of [6,6-$^2H_2$]-glucose tracer using other parameters

	including, but not limited to, C_{max}, T_{max}, T_{lag} and AUC over different time intervals. 7. To assess the safety of repeat administration of ORMD-0801 in patients with type 2 diabetes inadequately controlled on oral therapy.
Total Sample Size	Approximately 40 adult male and female subjects, aged 18 to 70 years, with T2DM.
Study Design	This study is designed to explore the efficacy of ORMD-0801 compared to placebo on endogenous glucose production in subjects with type 2 diabetes (T2DM). Subjects will undergo an initial Screening Visit (Visit 0) to establish their eligibility to participate in the study. At Visit 1 (2 weeks after the Screening Visit), qualifying subjects will be randomized to either ORMD-0801 (8 mg) or matching placebo, study medication will be dispensed and subjects will dose twice a day, once in the morning prior to breakfast and once at night prior to bedtime. Doses will occur at 45 minutes (± 15 minutes) before breakfast) and no later than 10 AM each morning, and at 8 PM (± 120 minutes) each night, and no sooner than 1 hour after dinner. Subjects will return to the clinic, 2 weeks later, for Visit 2. At this visit, subject compliance will be assessed, medication will be dispensed, a blood sample will be collected to measure HbA1c and subjects will be questioned for any adverse events. Subjects will be scheduled to return to the clinic in 2 weeks for morning admission (8 AM ± 120 minutes) to the PK unit (Visit 3). Subjects will be provided with standardized meals and the morning dose in-clinic. A light standardized dinner meal will be provided at 6 PM ± 30 minutes. At approximately 8 PM (± 60 minutes, and no sooner than 1 hour after dinner), subjects will be dosed with their study medication and will be started on a 16-hour infusion of [6,6-$^2H_2$]-glucose tracer. Blood samples will be collected to measure endogenous glucose (tracer attached), plasma glucose, metabolites and hormones for the duration of the infusion. Blood samples will be drawn at baseline (pre-infusion), 45, 90, 120 and 150 minutes, and 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 hours. Subjects will be required to remain fasting from the evening of Day 28 until the end of the infusion. Water intake will be unrestricted. On Day 29, blood sample will also be collected to measure HbA1c. Following completion of the infusion, the subjects will receive a standardized lunch and will be observed for an additional 6 hours. Prior to discharge, a physical examination will be performed, and blood/urine samples will be collected for safety chemistry, hematology and urinalysis, following which subjects will be discharged from the CRU and will exit the study.
Primary Endpoint	1. Difference in endogenous glucose production between active and placebo as measured by the glucose with tracer attached using $AUC_{(0-16)}$ as the primary parameter.

Secondary Endpoints	1. Mean changes in HbA1c from baseline to Day 29 of the treatment period. 2. Mean changes plasma glucose levels from baseline to Day 29 of the treatment period. 3. Mean changes in ketones from baseline to Day 29 of the treatment period. 4. Mean Changes in FFA from baseline to Day 29 of the treatment period. 5. Mean change in TC, LDLC, HDLC and TG from baseline to Day 29 of the treatment period. 6a. Difference in endogenous glucose production between active and placebo as measured by the glucose with tracer attached using other parameters including, but not limited to: a. $AUC_{(0-2)}$, $AUC_{(0-4)}$, $AUC_{(0-8)}$, $AUC_{(0-12)}$, b. $AUC_{(2-16)}$, $AUC_{(4-16)}$, $AUC_{(8-16)}$, $AUC_{(12-16)}$, c. C_{max}, d. T_{max}, and e. T_{lag}. 6b. Difference in metabolites (β-hydroxybutyrate, acetoacetate, lactate, pyruvate, FFA, glycerol) and hormones (insulin, C-peptide, glucagon) between active and placebo using the same AUC intervals as endogenous glucose production. 7. Safety assessed by adverse event reporting including adverse events of special significance such as hypoglycemia.
Duration of Participation	Subjects will be evaluated for participation in the study during a 1 to 3-week Screening period. Following Screening, eligible subjects will enter a 4-week double blind treatment period.
Subject Selection Criteria	**Inclusion criteria** 1. Male and female subjects aged, 18 - 70 years. 2. Established diagnosis of T2DM for at least 6 months prior to Screening, with HbA1c $\geq$ 7.5%. and $\leq$ 11%. 3. Stable dose of metformin (at least 1500 mg or maximal tolerated dose) for a period of at least 3 months prior to Screening. 4. Taking metformin only or metformin in addition to no more than two of the following: DPP-4, SGLT-2, or TZD. 5. Body mass index (BMI) of up to 35 kg/m^2 at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening. 6. Renal function – eGFR > 30 ml/min/1.73 m^2.

	7. Females of childbearing potential must have a negative serum pregnancy test result at Screening. a. 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); ii. Has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR iii. Has a congenital or acquired condition that prevents childbearing. b. Females of childbearing potential agree to avoid becoming pregnant while receiving study treatment and for 14 days after the last dose of study treatment by complying with one of the following: i. Practice abstinence† from heterosexual activity; OR ii. Use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡: 1. Single method (one of the following is acceptable): a. Non-hormonal intrauterine device (IUD); b. vasectomy of a female subject's male partner. 2. Combination method (requires use of two of the following): a. diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide); b. cervical cap with spermicide (nulliparous women only); c. contraceptive sponge (nulliparous women only); d. male condom or female condom (cannot be used together). †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. If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method

	of contraception for subjects participating at sites in this country/region. **Exclusion criteria** 1. Subjects with insulin-dependent diabetes: a. Has a history of type 1 diabetes mellitus or a history of ketoacidosis, or subject is assessed by the investigator as possibly having type 1 diabetes mellitus confirmed by a C-peptide < 0.7 ng/mL (0.23 nmol/L). b. Has a history of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant). 2. Treatment with glucosidase inhibitor, insulin secretagogues (other than sulfonylureas), glucagon-like peptide 1 (GLP-1) agonists within 3 months prior to Visit 1. 3. History of any basal, pre-mix or prandial insulin (greater than 7 days) within 6 months prior to Screening. 4. History of > 2 episodes of severe hypoglycemia within 6 months prior to Screening. 5. History of hypoglycemic unawareness (episodes of severe hypoglycemia with seizure or requiring third party intervention or documented low blood glucose without associated autonomic symptoms). 6. Subjects with the following secondary complications of diabetes: a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy/retinal photography examination performed (by a qualified person as per the country legislation) within 6 months prior to Screening. b. Renal dysfunction: estimated creatinine clearance < 30 ml/min. c. History of proliferative retinopathy or severe form of neuropathy or cardiac autonomic neuropathy (CAN). d. Uncontrolled or untreated severe hypertension defined as systolic blood pressure above or equal to 180 mmHg and/or diastolic blood pressure above or equal to 120 mmHg. e. Presence of unstable angina or myocardial infarction within 6 months prior to Screening, Grade 3 or 4 congestive heart failure (CHF) according to the New York Heart Association (NYHA) criteria, valvular heart disease, cardiac arrhythmia requiring treatment, pulmonary hypertension, cardiac surgery, history/occurrence of coronary angioplasty and/or stroke or transient ischemic attack (TIA) within 6 months prior to Screening.

	7. Subjects with psychiatric disorders which, per investigator judgment, may have impact on the safety of the subject or interfere with subject's participation or compliance in the study. 8. Subjects who needed (in the last 12 months) or may require systemic (oral, intravenous, intramuscular) glucocorticoid therapy for more than 2 weeks during the study period. 9. Laboratory abnormalities at Screening including: a. C-peptide < 0.7 ng/mL (0.23 nmol/L). b. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or > 1.5X the upper limit of normal. c. Elevated liver enzymes (alanine transaminase (ALT), alanine aminotransferase (AST), alkaline phosphatase) > 2X the upper limit of normal. d. Very high triglyceride levels (> 600 mg/dL); a single repeat test is allowable. e. Any relevant abnormality that would interfere with the efficacy or the safety assessments during study treatment administration. 10. Positive history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic hepatitis B or C, primary biliary cirrhosis, or active symptomatic gallbladder disease. 11. Positive history of HIV. 12. Use of the following medications: a. History of any basal, pre-mix or prandial 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. Administration of systemic long-acting corticosteroids within two months or prolonged use (more than one week) of other systemic corticosteroids or inhaled corticosteroids (if daily dosage is > 1,000 µg equivalent beclomethasone) within 30 days prior to Screening. Intra-articular and/or topical corticosteroids are not considered systemic. d. Use of medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and inhaled steroids (as discussed above), and immunosuppressive or immunomodulating agents. 13. Known allergy to soy. 14. Subject is on a weight loss program and is not in the maintenance phase, or subject has started weight loss medication (e.g., orlistat or liraglutide), within 8 weeks prior to Screening.

	15. Subject has had bariatric surgery. 16. Subject is pregnant or breast-feeding. 17. 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. 18. Subject is smoking more than 10 cigarettes per day. 19. One or more contraindications to metformin as per local label. 20. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption. 21. At the Principal Investigator's discretion, any condition or other factor that is deemed unsuitable for subject enrollment into the study.
Statistical Methods	This study is a parallel design in which subjects will receive one of two treatments (ORMD-0801 8mg BID (active) or placebo). The primary endpoint of the study is based on a 16-hour infusion that is done once after 28 days of treatment. The analyses performed using information from the 16-hour Harmonisation infusion will be analyzed using an Analysis of Variance model with treatment as the main effect. Change from baseline analyses will be analyzed using an Analysis of Covariance model with treatment as the main effect and baseline value as the covariate.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice a day
BUN	blood urea nitrogen
CAN	cardiac autonomic neuropathy
CFR	Code of Federal Regulations
CHF	congestive heart failure
C_{max}	maximum concentration
CRO	contract research organization
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase 4
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
ET	early term
EW	early withdrawal
FDA	Food and Drug Administration
FFA	free fatty acid
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HDLC	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug application
IRB	Institutional Review Board
IUD	intrauterine device
LDLC	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PK	pharmacokinetic
SAE	serious adverse event
SBP	systolic blood pressure
SBTI	soybean trypsin inhibitor

SGLT-2	sodium-glucose co-transporter 2
SOP	standard operating procedure
TC	total cholesterol
TG	triglycerides
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum concentration
TIA	transient ischemic attack
T_{lag}	absorption lag time
TSH	serum thyrotropin
TZD	thiazolidinedione
T2DM	type 2 diabetes mellitus
WCBP	woman of childbearing potential
WHO	World Health Organization

1 INTRODUCTION

Endogenous insulin – secreted by the ß-cells of the endocrine pancreas – flows to the liver in the portal blood before reaching the systemic circulation through the hepatic veins. Following oral administration, the insulin in ORMD-0801 is absorbed through the gastrointestinal mucosa into the mesenteric veins (mostly, the superior mesenteric vein that drains blood from the jejunum and ileum) and reaches the liver *via* the portal vein, thereby mimicking the route of entry of endogenous insulin. The main action of insulin in the liver is to suppress glucose production; for this action, sensitivity is higher, and onset and offset time of this action are faster than for insulin stimulation of glucose uptake by peripheral tissues. First-pass extraction of insulin by the liver is 50-60%; recirculation raises this percentage to ~80%. As a consequence, portal plasma insulin concentrations normally are ~3-fold higher than peripheral insulin levels.

The hypothesis behind ORMD-0801 is that sufficient oral insulin survives gastrointestinal degradation to arrive at the liver where it inhibits glucose production and, through this effect, lowers fasting plasma glucose concentrations. As the majority of this exogenous insulin dose is degraded in the liver, the resulting systemic insulin levels may be only marginally increased, thereby avoiding the risk of hypoglycemia.

The use of glucose tracers is the standard non-invasive approach to measure endogenous glucose production (EGP) [1]. A tracer (in this protocol, [6,6-$^{2}H_{2}$]-glucose, a stable isotope of glucose) infused intravenously at a constant rate will equilibrate with endogenous glucose across its distribution space within ~3 hours. From this time onward, the ratio of the tracer infusion rate to the plasma tracer/tracee ratio (as assayed by GCMS) measures EGP. As compared to placebo, oral insulin is expected to reduce EGP over the ensuing 13 hours of continued fasting. In patients with type 2 diabetes, EGP is known to be abnormally elevated and to contribute the hyperglycemia [2]. Oral insulin is therefore addressing a key pathophysiological derangement of type 2 diabetes.

2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective:	**Primary Endpoint:**
1. To assess the differences in endogenous glucose production in subjects with type 2 diabetes treated for 4 weeks either with ORMD-0801 or matching placebo following an intravenous infusion of [6,6-2H2]-glucose tracer using AUC(0-last).	1. Difference in endogenous glucose production between active and placebo as measured by the glucose with tracer attached using $AUC_{(0-16)}$ as the primary parameter.
Secondary Objectives:	**Secondary Endpoints:**
1. To compare the change from baseline in HbA1c levels measured at Week 4 in type 2 diabetic patients treated for 4 weeks with either ORMD-0801 or matching placebo. 2. To compare the change from baseline in plasma glucose levels measured at Week 4 in type 2 diabetic patients treated for 4 weeks with either ORMD-0801 or matching placebo. 3. To compare the change from baseline in ketone levels measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 4. To compare the change from baseline in FFAs measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 5. To compare the change from baseline in TC, LDLC, HDLC, and TG measured at Week 4 in type 2 diabetics treated for 4 weeks with either ORMD-0801 or matching placebo. 6. To assess the differences in endogenous glucose production in patients with type 2 diabetes treated for 4 weeks either with ORMD-0801 or matching placebo following an intravenous infusion of [6,6-$^2H_2$]-glucose tracer using other parameters including, but not limited to, C_{max}, T_{max}, T_{lag} and AUC over different time intervals. 7. To assess the safety of repeat administration of ORMD-0801 in patients with type 2 diabetes inadequately controlled on oral therapy.	1. Mean changes in HbA1c from baseline to Day 29 of the treatment period. 2. Mean changes plasma glucose levels from baseline to Day 29 of the treatment period. 3. Mean changes in ketones from baseline to Day 29 of the treatment period. 4. Mean Changes in FFA from baseline to Day 29 of the treatment period. 5. Mean change in TC, LDLC, HDLC and TG from baseline to Day 29 of the treatment period. 6a. Difference in endogenous glucose production between active and placebo as measured by the glucose with tracer attached using other parameters including, but not limited to: a. $AUC_{(0-2)}$, $AUC_{(0-4)}$, $AUC_{(0-8)}$, $AUC_{(0-12)}$, b. $AUC_{(2-16)}$, $AUC_{(4-16)}$, $AUC_{(8-16)}$, $AUC_{(12-16)}$, c. C_{max}, d. T_{max}, and e. T_{lag}. 6b. Difference in metabolites (β-hydroxybutyrate, acetoacetate, lactate, pyruvate, FFA, glycerol) and hormones (insulin, C-peptide, glucagon) between active and placebo using the same AUC intervals as endogenous glucose production. 7. Safety assessed by adverse event reporting including adverse events of special significance such as hypoglycemia.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is designed to explore the efficacy of ORMD-0801 compared to placebo on endogenous glucose production in subjects with type 2 diabetes (T2DM). Subjects will undergo an initial Screening Visit (Visit 0) to establish their eligibility to participate in the study. At Visit 1 (2 weeks after the Screening Visit), qualifying subjects will be randomized to either ORMD-0801 (8 mg) or matching placebo, study medication will be dispensed and subjects will dose, twice a day, once in the morning prior to breakfast and once at night prior to bedtime. Doses will occur at 45 minutes (± 15 minutes) before breakfast and no later than 10 AM each morning, and at 8 PM (± 120 minutes) each night, and no sooner than 1 hour after dinner. Subjects will return to the clinic, 2 weeks later, for Visit 2. At this visit, subject compliance will be assessed, medication will be dispensed, a blood sample will be collected to measure HbA1c and subjects will be questioned for any adverse events. Subjects will be scheduled to return to the clinic in 2 weeks for morning admission (8 AM ± 120 minutes) to the PK unit (Visit 3). Subjects will be provided with standardized meals and the morning dose in-clinic. A light standardized dinner meal will be provided at 6 PM ± 30 minutes. At approximately 8 PM (± 60 minutes, and no sooner than 1 hour after dinner), subjects will be dosed with their study medication and will be started on a 16-hour infusion of [6,6-$^{2}H_{2}$]-glucose tracer. Blood samples will be collected to measure endogenous glucose (tracer attached), plasma glucose, metabolites and hormones for the duration of the infusion. Blood samples will be drawn at baseline (pre-infusion), 45, 90, 120 and 150 minutes, and 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 hours (see Table 2 for blood draw schedule). Subjects will be required to remain fasting from the evening of Day 28 until the end of the infusion. Water intake will be unrestricted. On Day 29, blood sample will also be collected to measure HbA1c. Following completion of the infusion, the subjects will receive a standardized lunch and will be observed for an additional 6 hours. Prior to discharge, a physical examination will be performed, and blood/urine samples will be collected for safety chemistry, hematology and urinalysis, following which subjects will be discharged from the CRU and will exit the study.

3.2 Screening/Visit 0 (Week -3 to -1, Day -21 to -7)

At the Screening Visit (Visit 0), 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 which 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 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 morning following a 10-hour fast. Screening activities after obtaining informed consent will be conducted and consist of the following:

- Demographics (sex, age, race and ethnicity);
- Completion of medical and social history, including tobacco, alcohol, caffeine and drug use.
- Review of prior and current medications and supplements;
- Review of inclusion and exclusion criteria;
- Physical examination;
- 12-lead electrocardiogram (ECG);
- Measurement of height, weight and BMI;
- Measurement of vital signs (SBP/DBP and heart rate);
- Collection of fasted blood and urine samples for clinical safety labs:
    - Hematology, serum chemistry and urinalysis (see Section 6.1.5.1 for list of tests);
    - HbA1c;
    - Urine drug screen;
    - Serum pregnancy test (women of childbearing potential/WCBP only);
- Breathalyzer;
- Blood plasma sample will be collected for the assessment of plasma glucose, metabolites and hormones listed in the footnote of Table 2;
- Remind subjects to arrive fasting for Visit 1 in 2 weeks.

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 (Visit 0) through Visit 3);
- minimal use of concomitant medications during the study, if possible, 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;
- 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.

3.2.1 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 4.3 of this protocol (note that this includes assessments prior to receiving treatment on Visit 1) and was not randomized to receive 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 data collected for that subject during the screening process will be entered into the EDC system.

3.3 Treatment Period

The Treatment Period will last for 4 weeks from Visit 1 (Day 0) to Visit 3 (Day 28).

3.3.1 Visit 1 (Week 0, Day 0)

Subjects will report to the clinic in morning following a 10-hour fast. At Visit 1, the following procedures will be performed:

- Review of inclusion and exclusion criteria;
- Review of prior and current medications and supplements;
- Measurement of vital signs (SBP/DBP and heart rate);
- Measurement of weight;
- Breathalyzer;
- Subjects will be randomized to either ORMD-0801 (8 mg) or placebo. Subjects will be instructed to dose twice a day. Doses will occur at 45 minutes (± 15 minutes) before breakfast and no later than 10 AM each morning, and at bedtime (@ 8 PM ± 120 minutes) each night, and no sooner than 1 hour after dinner;
- Study medication will be dispensed;
- Blood sample will be collected to measure HbA1c;
- AEs/SAEs assessment;
- Remind subjects to arrive fasting for Visit 2 in 2 weeks.

3.3.2 Visit 2 (Week 2, Day 14)

Subjects will report to the clinic in morning following a 10-hour fast. At Visit 2, the following procedures will be performed:

- Review of prior and current medications and supplements;
- Measurement of vital signs (SBP/DBP and heart rate);
- Measurement of weight;
- Breathalyzer;
- Study medication will be collected, and compliance will be reviewed;
- Study medication will be dispensed;
- Blood sample will be collected to measure HbA1c;
- AEs/SAEs assessment;
- Remind subjects to arrive fasting for Visit 3 in 2 weeks.

3.4 Tracer Infusion

3.4.1 Visit 3 (Week 4, Day 28)

Subjects will report to the clinic in morning following a 10-hour fast. At Visit 3 (Day 28), the following procedures will be performed:

- Admission to the CRU (8 AM ± 120 minutes);
- Review of prior and current medications and supplements;
- Measurement of vital signs (SBP/DBP and heart rate);
- Measurement of weight;
- Breathalyzer;
- Urine pregnancy test (women of childbearing potential/WCBP only);
- Fasting blood sample will be collected to measure HbA1c;
- Study medication will be collected, and compliance will be reviewed;
- Subjects will be provided with a standard breakfast, lunch and dinner. The morning dose will be administered 45 minutes (± 15 minutes) before breakfast and no later than 10 AM, in-clinic. A light standardized dinner meal will be provided at 6 PM ± 30 minutes.
- Subjects will be dosed in-clinic with either ORMD-0801 (8 mg) or placebo (@ 8 PM ± 60 minutes) and started on a 16-hour infusion of [6,6-$^{2}H_2$]-glucose tracer immediately following dosing;
- Blood samples will be collected to measure endogenous glucose (tracer attached), plasma glucose, metabolites and hormones for the duration of the infusion. Blood samples will be drawn at baseline (pre-infusion), 45, 90, 120 and 150 minutes, and 3 and 4 hours (see blood draw schedule in Table 2). Subjects will be required to remain fasting from the evening of Day 28 (following dinner) until the end of the infusion;
- A backup blood sample will be collected at baseline (pre-infusion);
- AEs/SAEs assessment.

3.5 Discharge/End of Study

3.5.1 Visit 3 (Week 4, Day 29)

At Visit 3 (Day 29), the following procedures will be performed:

- Review of prior and current medications and supplements;
- Physical examination;
- Measurement of vital signs (SBP/DBP and heart rate);
- Fasting blood sample will be collected to measure HbA1c;
- Collection of fasted blood and urine samples for clinical safety labs for hematology, serum chemistry and urinalysis (see Section 6.1.5.1 for list of tests);
- Blood samples will be collected to measure endogenous glucose (tracer attached), plasma glucose, metabolites and hormones for the duration of the infusion. Blood samples will be drawn at 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 and 16 hours (see blood draw schedule in Table 2). Subjects will be required to remain fasting from the evening of Day 28 (following dinner) until the end of the infusion;

- A backup blood sample will be collected 16-hour after infusion;
- After completion of the infusion, subjects will be provided with a standard lunch;
- AEs/SAEs assessment;
- Following the 6-hour observation and end of study procedures, subjects will be discharged from the CRU in the evening.

3.6 Early Withdrawal (EW)

If a randomized subject is withdrawn from the study prior to completion, the subject will be instructed to return to the clinic the next day and will have the early term (ET) visit procedures completed. Subjects will then be discharged from the study. Subjects will report to the clinic in morning following a 10-hour fast. Subjects will complete the following evaluations:

- Review of prior and current 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 safety labs for hematology, serum chemistry and urinalysis (see Section 6.1.5.1 for list of tests);
- AEs/SAEs assessment;
- Discharge from CRU, if applicable.

Any subject with a possible study treatment related AE at the time of EW will be followed until resolution or stabilization of the event.

3.7 Schedule of Events

Table 1 below describes the daily schedule of events from Screening (Visit 0) to Discharge/End of Study (Visit 3, Day 29).

Table 1: Schedule of Events from Screening (Visit 0) to Discharge/End of Study (Visit 3, Day 29).

	Screening	Treatment Period			Discharge / End of Study	Early Withdrawal
				TRACER Infusion		
Visit	**0**	**1**	**2**	**3**		
Week	**-3 to -1**	**0**	**2**	**4**		
Day	**-21 to -7**	**0**	**14**	**28**	**29**	
Informed Consent	X					
Inclusion/Exclusion	X	X				
Demographics (sex, age, race and ethnicity)	X					
Medical and Social History (including tobacco, alcohol, caffeine and drug use)	X					
Prior/Concomitant Medications	X	X	X	X	X	X
Physical Examination	X				X	X
12-lead ECG	X					
Height, Weight, BMI[1]	X	X	X	X		X
Vital Signs	X	X	X	X	X	X
Chemistry, Hematology, Urinalysis[2]	X				X[2]	X
Blood Collection for Plasma Glucose, Metabolites and Hormones[3]	X			X	X	
Urine Drug Screen	X					
Serum Pregnancy Test[4]	X					
Urine Pregnancy Test[4]				X		
Breathalyzer	X	X	X	X		

	Screening	Treatment Period			Discharge / End of Study	Early Withdrawal
				TRACER Infusion		
Visit	**0**	**1**	**2**	**3**		
Week	**-3 to -1**	**0**	**2**	**4**		
Day	**-21 to -7**	**0**	**14**	**28**	**29**	
HbA1c	X	X	X	X	X	
Randomization		X				
Dispense study medication		X	X			
Collect study medication and review for compliance			X	X		
CRU Admission				X		
In-Clinic Dosing				X		
TRACER Infusion[5]				X	X	
Blood Collection for Tracer Marked Glucose, Metabolites and Hormones[6]				X	X	
Standard Meals[7]				X	X	
CRU Discharge[8]					X[6]	X
Adverse Events		X	X	X	X	X
End of Study					X	X

[1] Weight will be measured at each visit. Height will be measured and BMI will be calculated at Screening.
[2] Blood draw will be performed after the 16-hour infusion is complete.
[3] A blood plasma sample will be collected at Screening and during infusion for assessment of plasma glucose, metabolites and hormones according to Table 2.
[4] Serum pregnancy test and urine pregnancy test will be performed for women of childbearing potential (WCBP) only.
[5] Subjects will be started on a 16-hour infusion of TRACER immediately following dosing. Refer to Appendix A (Guidelines for TRACER Infusion).
[6] Blood samples will be collected during the duration of infusion based on the blood draw schedule in Table 2.
[7] A standard breakfast, lunch, and dinner will be provided on Day 28. Subjects will fast following dinner on Day 28 until the completion of the 16-hour infusion on Day 29. After completion of the infusion, subjects will be provided with a standard lunch.
[8] Following the 6-hour observation and end of study procedures, subjects will be discharged from the CRU in the evening of Day 29.

Table 2: Blood Draw Schedule

additive	EDTA+NaF	EDTA	EDTA	EDTA+30 µL diprotin+20 µL Foy°	EDTA+30 µL diprotin+20 µL Foy°	
assay	**Tracer**	**Glucose**	**Metabolites#**	**Hormones§**	**Backup**	***total***
Time	**mL**	**mL**	**mL**	**mL**	**mL**	***mL***
Baseline*	2	1	3	3	4	13
45 min	2	1	3	3		9
90 min	2	1	3	3		9
120 min	2	1	3	3		9
150 min	2	1	3	3		9
3 hours	2	1	3	3		9
4 hours	2	1	3	3		9
5 hours	2	1	3	3		9
6 hours	2	1	3	3		9
7 hours	2	1	3	3		9
8 hours	2	1	3	3		9
9 hours	2	1	3	3		9
10 hours	2	1	3	3		9
11 hours	2	1	3	3		9
12 hours	2	1	3	3		9
13 hours	2	1	3	3		9
14 hours	2	1	3	3		9
15 hours	2	1	3	3		9
16 hours	2	1	3	3	4	13
Total	***38***	***19***	***57***	***57***	***8***	***179***

* before starting tracer infusion
° Foy master solution = 0.035 mg in 10 mL of saline
ß-hydroxybutyrate, acetoacetate, lactate, pyruvate, FFA, glycerol
§ insulin, C-peptide, glucagon

4 STUDY SUBJECT SELECTION

4.1 Inclusion Criteria

1. Male and female subjects aged, 18 - 70 years.
2. Established diagnosis of T2DM for at least 6 months prior to Screening, with HbA1c ≥ 7.5%. and ≤ 11%.
3. Stable dose of metformin (at least 1500 mg or maximal tolerated dose) for a period of at least 3 months prior to Screening.
4. Taking metformin only or metformin in addition to no more than two of the following: DPP-4, SGLT-2, or TZD.
5. Body mass index (BMI) of up to 35 kg/m^2 at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening.
6. Renal function – eGFR > 30 ml/min/1.73 m^2.
7. Females of childbearing potential must have a negative serum pregnancy test result at Screening.
   a. 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);
      ii. Has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR
      iii. Has a congenital or acquired condition that prevents childbearing.
   b. Females of childbearing potential agree to avoid becoming pregnant while receiving study treatment and for 14 days after the last dose of study treatment by complying with one of the following:
      i. Practice abstinence† from heterosexual activity; OR
      ii. Use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡:
         1. Single method (one of the following is acceptable):
            a. Non-hormonal intrauterine device (IUD);
            b. vasectomy of a female subject's male partner.
         2. Combination method (requires use of two of the following):
            a. diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide);
            b. cervical cap with spermicide (nulliparous women only);
            c. contraceptive sponge (nulliparous women only);
            d. male condom or female condom (cannot be used together).

†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.

If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

4.2 Exclusion Criteria

1. Subjects with insulin-dependent diabetes:
   a. Has a history of type 1 diabetes mellitus or a history of ketoacidosis, or subject is assessed by the investigator as possibly having type 1 diabetes mellitus confirmed by a C-peptide < 0.7 ng/mL (0.23 nmol/L).
   b. Has a history of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).
2. Treatment with glucosidase inhibitor, insulin secretagogues (other than sulfonylureas), glucagon-like peptide 1 (GLP-1) agonists within 3 months prior to Visit 1.
3. History of any basal, pre-mix or prandial insulin (greater than 7 days) within 6 months prior to Screening.
4. History of > 2 episodes of severe hypoglycemia within 6 months prior to Screening.
5. History of hypoglycemic unawareness (episodes of severe hypoglycemia with seizure or requiring third party intervention or documented low blood glucose without associated autonomic symptoms).
6. Subjects with the following secondary complications of diabetes:
   a. Active proliferative retinopathy as confirmed by a dilated ophthalmoscopy/retinal photography examination performed (by a qualified person as per the country legislation) within 6 months prior to Screening.
   b. Renal dysfunction: estimated creatinine clearance < 30 ml/min.
   c. History of proliferative retinopathy or severe form of neuropathy or cardiac autonomic neuropathy (CAN).
   d. Uncontrolled or untreated severe hypertension defined as systolic blood pressure above or equal to 180 mmHg and/or diastolic blood pressure above or equal to 120 mmHg.
   e. Presence of unstable angina or myocardial infarction within 6 months prior to Screening, Grade 3 or 4 congestive heart failure (CHF) according to the New York Heart Association (NYHA) criteria, valvular heart disease, cardiac arrhythmia requiring treatment, pulmonary hypertension, cardiac surgery, history/occurrence of coronary angioplasty and/or stroke or transient ischemic attack (TIA) within 6 months prior to Screening.
7. Subjects with psychiatric disorders which, per investigator judgment, may have impact on the safety of the subject or interfere with subject's participation or compliance in the study.
8. Subjects who needed (in the last 12 months) or may require systemic (oral, intravenous, intramuscular) glucocorticoid therapy for more than 2 weeks during the study period.
9. Laboratory abnormalities at Screening including:

a. C-peptide < 0.7 ng/mL (0.23 nmol/L).

b. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or > 1.5X the upper limit of normal.

c. Elevated liver enzymes (alanine transaminase (ALT), alanine aminotransferase (AST), alkaline phosphatase) > 2X the upper limit of normal.

d. Very high triglyceride levels (> 600 mg/dL); a single repeat test is allowable.

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

10. Positive history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic hepatitis B or C, primary biliary cirrhosis, or active symptomatic gallbladder disease.
11. Positive history of HIV.
12. Use of the following medications:

    a. History of any basal, pre-mix or prandial 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. Administration of systemic long-acting corticosteroids within two months or prolonged use (more than one week) of other systemic corticosteroids or inhaled corticosteroids (if daily dosage is > 1,000 μg equivalent beclomethasone) within 30 days prior to Screening. Intra-articular and/or topical corticosteroids are not considered systemic.

    d. Use of medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and inhaled steroids (as discussed above), and immunosuppressive or immunomodulating agents.

13. Known allergy to soy.
14. Subject is on a weight loss program and is not in the maintenance phase, or subject has started weight loss medication (e.g., orlistat or liraglutide), within 8 weeks prior to Screening.
15. Subject has had bariatric surgery.
16. Subject is pregnant or breast-feeding.
17. 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.
18. Subjects is smoking more than 10 cigarettes per day.
19. One or more contraindications to metformin as per local label.
20. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption.
21. At the Principal Investigator's discretion, any condition or other factor 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 that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study.
6. Episodes of hypoglycemia not responsive to changes in diet or dose regimen (Section 7.4.3)
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 that in the judgment of the Investigator poses unacceptable risk to the subject.

Subjects who withdraw from the study may be replaced at the discretion of the investigator and will be discussed on a case-by-case basis.

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 as a result 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.

In the event that 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, in order to ensure that he/she is in satisfactory health. If a subject withdraws from the study as a result of meeting discontinuation criteria after the start of study treatment administration, reasonable efforts should be made to have the subject return for the

early withdrawal evaluations (Section 3.6). 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 between 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.

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

Dosage form: 1 soft gel capsule per dose to be administered twice daily

Strength: 8 mg insulin per capsule

Description: Soft gel capsule [SBTI, disodium EDTA, fish oil, aerosol, and Tween 80], Recombinant Human Insulin

Placebo control:

Fish oil in capsules, identical in appearance to ORMD-0801, administered twice daily

5.1.1 Packaging and Labeling

All study medication will be shipped in bulk. The unblinded investigational site pharmacist or designee will be responsible for dispensing the appropriate study treatment based on the

randomization schedule. Study medication will be distributed at each visit sufficient to cover the time between visits. Subjects will receive one bottle each at Visit 1 and Visit 2 to self-administer doses at home. Subjects will be dosed in-clinic from a new bottle at Visit 3.

Study medication will be dispensed to the site with instructions for when treatment can be administered. Unused study medication will be returned or destroyed according to instructions provided by Oramed Ltd.

The treatment packages will be labeled with the following information:

- Study number
- 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 label with the identical information will be made available 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 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. IMP will be returned or destroyed according to instructions provided by Oramed Ltd. Drug destruction procedures and documentation must be retained at the site.

5.2 Randomization

This is a randomized, double blind, parallel study. Approximately 40 subjects with T2D will be randomized to one of two treatment groups.

Integrium, LLC will generate and implement the randomization procedures for this trial. A computer-generated randomization schedule will be used for assigning the treatment groups. The Investigational Site pharmacist will follow this randomization schedule to dispense the appropriate study treatment.

5.3 Study Treatment Administration

5.3.1.1 Double-Blind Treatment Administration

All subjects will receive double-blind placebo or ORMD-0801 (8 mg insulin) twice a day, once in the morning and once in the evening, according to their randomization schedule from Visit 1 (Day 0) to Visit 3 (Day 28). Subjects will take one capsule (active or placebo), 45 minutes (± 15 minutes) before breakfast and no later than 10 AM each morning, and one capsule at 8 PM (± 120 minutes at Visits 1-2 and ± 60 minutes at Visit 3) each night, and no sooner than 1 hour after dinner.

5.4 Measuring Subject Compliance

Dosing compliance will be assessed through a count of unused study medication at each clinic visit.

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 in the eCRF.

5.6 Concomitant Medications and Supplements

All medications and supplements (other than study treatment) taken by the subject from Visit 1 through Visit 3 will be considered "concomitant" medications and supplements. Medications and supplements taken prior to Visit 1 that 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 course of 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 Visit 3;
2. Any anti-diabetic drugs (except for those allowable by the inclusion criteria) including insulin, GLP-1 analogue, α-glucosidase inhibitors, glinides, and pramlintide unless required for rescue;
3. Thyroid preparations or thyroxine (except in subjects on stable replacement therapy);

4. Systemic long-acting corticosteroids or other systemic corticosteroids or inhaled corticosteroids (if daily dosage is > 1,000 μg equivalent beclomethasone). Intra-articular and/or topical corticosteroids are not considered systemic.
5. Medications known to modify glucose metabolism or to decrease the ability to recover from hypoglycemia such as oral, parenteral, and inhaled steroids, and immunosuppressive or immunomodulating agents.

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 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, and for concomitant medications and supplements, this indication must be represented as either for the treatment of an AE, for 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 course of the study may be treated for that condition. If the condition is suspected during Screening (Visit 0), 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 should arrive following a minimum 10-hour fast to the clinic as described in the study design. All subjects will continue with their regular diet. Subjects will fast from the evening of Visit 3, Day 28, until the end of infusion. Water intake will be unrestricted.

Excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) will not be allowed from Screening (Visit 0) through Visit 3. Excessive alcohol use or binge drinking will be discouraged during the study, and alcohol will be prohibited 72 hours prior to each visit). Subjects must refrain from smoking more than 10 cigarettes per day. Subject should not use any recreational or illicit drugs within one year prior to Screening through Visit 3.

Subjects will also be asked to refrain from any unusual or unaccustomed vigorous exercise during the course of the study.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 Safety Assessments

6.1.1 Weight, Height and BMI

Weight, height and BMI will be measured at every visit (Table 1). 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.

6.1.2 Vital Signs

Vital signs (including seated SBP/DBP and heart rate) will be recorded at all visits as described in Table 1. 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 1 or Early Withdrawal. 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 at Screening (Table 1). 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 (Federicia's) intervals and clinically significant abnormalities.

6.1.5 Clinical Laboratory Tests

Fasted blood and urine samples for clinical safety laboratory assessments will be collected and processed using standard procedures as indicated in Table 1. Laboratory samples will be processed by appropriate laboratories.

In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant.

6.1.5.1 Clinical Safety Labs

The clinical safety labs will include the following hematology, serum chemistry and urinalysis 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

Serum Chemistry

- Sodium
- Potassium
- Chloride
- Bicarbonate
- ALT
- AST
- Gamma-glutamyltransferase (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)

Urinalysis

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

6.1.5.2 Pregnancy Test

A serum pregnancy test will be performed for women of child-bearing potential (WCBP) at Screening. A urine pregnancy test will be performed for WCBP at Visit 3 (Day 28) (Table 1).

6.1.5.3 Urine Drug Test

A urine drug test will be performed for drugs of abuse at Screening as indicated in Table 1. These will include testing for amphetamines, barbiturates, cocaine metabolites, opiates, and benzodiazepines.

6.2 Efficacy Assessments

6.2.1 16-Hour Tracer Infusion

A 16-hour tracer infusion will be performed after 28 days of treatment. The blood draw schedule during the tracer infusion is documented in Table 2 in Section 3.7 of the protocol. Based on the blood draws the values for the following lab tests will be obtained:

- Endogenous Glucose Production (glucose that is produced by the liver which has the tracer attached),
- Key metabolites (β-hydroxybutyrate, acetoacetate, lactate, pyruvate, FFA, glycerol), and
- Key hormones (insulin, C-peptide, glucagon).

For each of the lab tests, the following parameters will be derived (as appropriate):

- $AUC_{(0-16)}$,
- $AUC_{(0-2)}$, $AUC_{(0-4)}$, $AUC_{(0-8)}$, $AUC_{(0-12)}$,
- $AUC_{(2-16)}$, $AUC_{(4-16)}$, $AUC_{(8-16)}$, $AUC_{(12-16)}$,
- C_{max} (endogenous glucose production only),
- T_{max} (endogenous glucose production only), and
- T_{lag} (endogenous glucose production only).

6.2.2 Hemoglobin A1c (HbA1c)

Hemoglobin A1c will be collected at every visit.

6.2.3 Plasma Glucose Levels

Plasma glucose levels will be collected prior to dosing and after 28 days of dosing. The plasma glucose levels collected after the 16-hour infusion period is complete is the value that will be analyzed for this test.

6.2.4 Ketones and Free Fatty Acids

Ketones and free fatty acid levels will be collected prior to dosing and after 28 days of dosing. The values collected after the 16-hour infusion period is complete are the values that will be analyzed for these tests.

6.2.5 Lipids (Total Cholesterol, LDL Cholesterol, HDL Cholesterol and Triglycerides)

Lipids will be collected prior to dosing and after 28 days of dosing. The values collected after the 16-hour infusion period is complete are the values that will be analyzed for these tests.

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) and clinical safety labs (hematology, serum chemistry and urinalysis).

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 course of 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 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 subject and may require 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 or 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.

7.4 Eliciting and Reporting of Adverse Events

AE monitoring will start immediately following the first dose of active treatment or placebo (Visit 1) and will continue through Visit 3. Any subject with a possible study treatment-related AE at the end of the study will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related 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. In order to avoid bias in eliciting AEs, subjects will be asked general, non-leading questions such as "How are you feeling?"

All AEs, including 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 Screening 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 Visit 1. 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.

7.4.1 Routine Reporting of Adverse Events

All AEs, whether or not associated with the study treatment, that are observed by the Investigator, other Investigational Site personnel, or those reported by 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 7.4.2 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 7.3), and if so, the reason it is considered serious;
- Severity of AE (per definition in Section 7.6);
- Assessment of the attributability of the AE to the study treatment [per definition in Section 7.4];
- Whether the event is expected (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 7.8).

7.4.2 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. The contact information for the Medical Monitor is provided below.

Medical Monitor:
Carmen Margaritescu, MD
Safety Office, Integrium, LLC
Office: 714-210-6665
Cellular: 714-328-7083
Email: carmen.margaritescu@integrium.com

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 serious adverse events, the Investigator must to 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 adverse event 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 7.8) and possibly related to the study treatment (s) (i.e., an adverse reaction or suspected adverse reaction as defined in Section 7.6), in the opinion of either the Investigator or the Medical Monitor, the blind will be broken for the subject that experiences the event. If the Investigational Site personnel need to unblind the study treatment they can contact the unblinded programmer and pharmacist.

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 to 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.

7.4.2.1 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 Integrium 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.

7.4.3 Adverse Events of Hypoglycemia

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.

Due to the specific relevance of hypoglycemia as a limiting factor in insulin therapy, AEs of hypoglycemia will be reviewed at every visit. All hypoglycemic events will be reported on a special hypoglycemia AE eCRF page. This will include the following information:

- Subject symptoms;
- Type of symptoms;
- BG value during the hypoglycemic event and the event severity based on CTCAE criteria;
- Whether treatment was required;
- Whether assistance was required for treatment;
- What specific treatment, if any, was used.

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, such as BG < 70 mg/dL and < 53 mg/dL for example.

7.4.4 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 investigative site for follow-up.

7.5 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.

7.6 Adverse Event Severity Assessment

The severity of each AE will be graded according to the NCI CTCAE, version 4.03. 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 7.3.

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

7.8 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 or not related 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.

7.9 Clinical Findings

Any significant clinical findings at Visit 3 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 7.4), 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-018. Additional details will be provided in the statistical analysis plan.

8.1 Study Design

The primary analysis is a comparison of difference in endogenous glucose production for the ORMD-0801 treated group and placebo. Let pC be the endogenous glucose production for the control (placebo) arm and let pT be the endogenous glucose production for the treatment (ORMD-0801) arm. The primary analysis is:

$$H0 : pC=pT$$

$$H1 : pC\neq pT$$

Trial success is defined as having the endogenous glucose production for the placebo group being greater than the endogenous glucose production for the ORMD-0801 treated group.

8.2 Sample Size

Sample size determination was not based on statistical considerations.

8.3 Primary Efficacy Evaluation

The primary endpoint for this study is the difference in endogenous glucose production between active and placebo as measured by the glucose with tracer attached using $AUC_{(0-16)}$.

The primary endpoint will be analyzed using an Analysis of Variance model with treatment as the main effect.

8.4 Secondary Efficacy Evaluation

8.4.1 16-Hour Tracer Infusion

A 16-hour tracer infusion will be performed after 28 days of treatment. The blood draw schedule during the tracer infusion is documented in Table 2 in Section 3.7 of the protocol. Based on the blood draws the values for the following lab tests will be obtained:

- Endogenous Glucose Production (glucose that is produced by the liver which has the tracer attached),
- Key metabolites (β-hydroxybutyrate, acetoacetate, lactate, pyruvate, FFA, glycerol), and
- Key hormones (insulin, C-peptide, glucagon).

For each of the lab tests, the following parameters will be derived (as appropriate):

- $AUC_{(0-16)}$,
- $AUC_{(0-2)}$, $AUC_{(0-4)}$, $AUC_{(0-8)}$, $AUC_{(0-12)}$,
- $AUC_{(2-16)}$, $AUC_{(4-16)}$, $AUC_{(8-16)}$, $AUC_{(12-16)}$,

- C_{max} (endogenous glucose production only),
- T_{max} (endogenous glucose production only), and
- T_{lag} (endogenous glucose production only).

Each of these parameters for each of the tests will be analyzed using an Analysis of Variance model with treatment as the main effect.

8.4.2 Hemoglobin A1c (HbA1c)

Hemoglobin A1c will be collected prior to dosing and after 28 days of dosing. This parameter will be analyzed using an Analysis of Covariance model with treatment as the main effect and baseline value as the covariate.

8.4.3 Plasma Glucose Levels

Plasma glucose levels will be collected prior to dosing and after 28 days of dosing. The plasma glucose levels collected after the 16-hour infusion period is complete, is the value that will be analyzed for this test. This parameter will be analyzed using an Analysis of Covariance model with treatment as the main effect and baseline value as the covariate.

8.4.4 Ketones and Free Fatty Acids

Ketones and free fatty acid levels will be collected prior to dosing and after 28 days of dosing. The values collected after the 16-hour infusion period is complete, are the values that will be analyzed for these tests. These parameters will be analyzed using an Analysis of Covariance model with treatment as the main effect and baseline value as the covariate.

8.4.5 Lipids (Total Cholesterol, LDL Cholesterol, HDL Cholesterol and Triglycerides)

Lipids will be collected prior to dosing and after 28 days of dosing. The values collected after the 16 hour infusion period is complete, are the values that will be analyzed for these tests. These parameters will be analyzed using an Analysis of Covariance model with treatment as the main effect and baseline value as the covariate.

8.5 Safety Evaluation

8.5.1 Safety Population

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

8.5.2 Adverse Events

AEs will be coded using the most current version of MedDRA.

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 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.

TEAEs that lead to withdrawal from the study will be separately listed and summarized.

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.

8.5.3 Laboratory Evaluations

Individual clinical safety lab (hematology, serum chemistry, and urinalysis) 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 (Screening) in laboratory values will be calculated and summarized descriptively. A clinically significant change from baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.5.4 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 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.

8.5.5 12-lead ECG

Individual 12-lead ECG assessments are only collected as screening and will be listed.

8.5.6 Physical Examination

Individual physical examination findings will be listed by visit. A clinically significant change from baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.5.7 Prior and Concomitant Medications and Supplements

Medications and supplements will be coded using the most current version of the WHO Drug Reference List, 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 stopped within 30 days prior to the first dose of study treatment. The incidence of these prior and concomitant medications and supplements will be summarized.

8.5.8 Handling of Missing, Unused, or Spurious Data

Descriptive statistics and listings will be provided for all data. No substitution of missing data will be used in any calculations. Data points that appear to be spurious will be investigated and will not be excluded from the listings. Influential cases will be handled in an appropriate statistical manner.

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 (which 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 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 appropriate laboratories. Results will be reported to Integrium 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 or a random sample equal to 10% of subjects, with a minimum of 5 subjects 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, Integrium, 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 the 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 that 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 any and 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 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 as a result 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, to other pharmaceutical companies, to the FDA, and to 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 Electronic Data Capture

All data required by the study protocol will be recorded in the electronic database. Data from the source documents will be entered into the EDC system by authorized Investigational Site personnel. The data 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 are accurate and correct by electronically signing the subject's 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, as well as 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 of 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 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, to verify the accuracy and completeness of the eCRFs, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to 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 in order 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 Investigator's 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 in the course of the study are 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) not 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 Integrium in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor and Integrium (protocols, IBs, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor and Integrium to the Investigator may not be disclosed to others without direct written authorization from the Sponsor and Integrium, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

13 REFERENCES

1. Gastaldelli A, Baldi S, Pettiti M, Toschi E, Camastra S, Natali A, Landau BR, Ferrannini E. Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans: a quantitative study. Diabetes. 2000 Aug;49(8):1367-73.
2. Ferrannini E, Gastaldelli A, Iozzo P. Pathophysiology of prediabetes. Med Clin North Am. 2011 Mar;95(2):327-39.

14 APPENDIX A

14.1 Guidelines for TRACER Infusion

EGP Protocol

Tracer: [6,6-$^{2}H_2$]-glucose (from Cambridge Isotope Laboratories [https://shop.isotope.com/productdetails.aspx?itemno=DLM-349-PK])

Constant tracer infusion rate: 0.28 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ (= 51 $\mu g \cdot min^{-1} \cdot kg^{-1}$) *via* an indwelling catheter in an antecubital vein. Assuming participants have dinner at 18:00pm, the tracer infusion can start at 20:00pm and continue until 12 noon the following day, *i.e.*, for 960 min.

Example: In a T2D subject weighing 90 kg, the total amount of tracer would be 0.28 *x* 960 *x* 90 = 24,192 µmol (= 4.41 g per study). Rounding this up, on dissolves 4.5 g of [6,6-$^{2}H_2$]-glucose in 500 mL of saline: this is the mother solution (from which a 5 mL aliquot must be saved together with the plasma samples) to be given at a rate of 0.5 mL/min to the 90-kg person for 960 min.

Blood sampling: through a cannula in a contralateral antecubital vein, one sample is taken prior to starting the tracer infusion, then blood is drawn every hour till the end.