Clinical Study Protocol: ORA-D-015

Study Title:	A Placebo-controlled, Multi-center, Randomized, Phase 2b Study to Evaluate the Efficacy and Safety of ORMD-0801 in Type 2 Diabetes Mellitus Patients with Inadequate Glycemic Control on Oral Therapy
Protocol Number:	ORA-D-015
Study Phase:	Phase 2b
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SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned has reviewed and approved Protocol No. ORA-D-015 for issuance:

M. Kidron
Signature

9-APRIL-2019
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 Placebo-controlled, Multi-center, Randomized, Phase 2b Study to Evaluate the Efficacy and Safety of ORMD-0801 in Type 2 Diabetes Mellitus Patients with Inadequate Glycemic Control on Oral Therapy
Indication	Type 2 Diabetes Mellitus (T2DM)
Clinical Phase	Phase 2b
Study Treatment	ORMD-0801 (insulin)
Dose	Cohort A: Begin at 16 mg/dose, titrate to 24 mg/dose, then titrate to 32 mg/dose Cohort B: 8 mg/dose or 16 mg/dose
Dosage Regimen	Cohort A: QHS, BID, or TID Cohort B: QHS or BID
Formulation	Soft gel capsule [SBTI, disodium EDTA, fish oil, aerosil, and Tween 80]
Mode of Administration	Oral
Primary Objective	To compare the efficacy of ORMD-0801 to placebo in improving glycemic control in T2DM subjects inadequately controlled on oral therapy based on HbA1C.
Secondary Objective	To assess the safety of repeat administration of ORMD-0801 in T2DM subjects inadequately controlled on oral therapy
Total Sample Size	Approximately 360 adult male and female subjects age 18 and older with T2DM.
Study Design	This study is designed to explore efficacy of ORMD-0801 when given in different regimens across a dose range for up to 12 weeks in subjects with type 2 diabetes mellitus (T2DM). Approximately 360 subjects with T2DM will initially undergo a 2-week, single-blind placebo run-in period (Visits 1 and 2), followed by a 12-week treatment period (Visits 3 through 9). For Cohort A, the total 12-week treatment period will include a Part 1"dose escalation" interval (2 weeks, Visits 3 and 4) and a Part 2 stable dose "maintenance" interval (10 weeks, Visits 5 through 9). The stable dose interval will be sufficient to allow for a robust assessment of treatment effect based on the mean change from baseline in HbA1C (A1C). For Cohort B, the total 12-week treatment period will include a stable dosing period for both Part 1 (2 weeks, Visits 3 and 4) and Part 2 (10 weeks, Visits 5 through 9). **Single-Blind Placebo Run-in:** During the placebo run-in period subjects will self- administer blinded placebo study medication at night prior to bedtime (@10 PM ± 90 minutes each night, no sooner than 2 hours after dinner). Outpatient glycemic levels and adverse events will be measured using self-monitored blood glucose (SMBG) and recorded in a diary. **Treatment Period:**

	Cohort A: Of the total 360 subjects, 265 will be randomized to one of the following four treatment arms: 1) ORMD-0801 once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) 2) ORMD-0801 twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast. 3) ORMD-0801 three times daily - TID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast and lunch. 4) Matched Placebo (either QHS, BID, or TID) In addition, per FDA request, the remaining 20 subjects will receive excipient matched placebo in a non-randomized single-blind fashion, TID, according to the same schedule as described above. Cohort B: Of the total 360 subjects, 75 will be randomized to one of the following five treatment arms: 1) ORMD-0801 8 mg once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) 2) ORMD-0801 8 mg twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast. 3) ORMD-0801 16 mg once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) 4) ORMD-0801 16 mg twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast. 5) Excipient matched placebo once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) **Part 1:** <u>Cohort A</u> In the first two weeks of active treatment (Part 1) subjects will receive double-blind therapy according to their randomized regimen (placebo or ORMD-0801) to be taken QHS, BID or TID. Subjects will undergo a step-wise dose escalation from a starting dose of 16 mg (Visit 3), to 24 mg (Visit 4), to a top dose of 32 mg (Visit 5 onward). Subjects will then enter Part 2. <u>Cohort B</u>

	In the first two weeks of active treatment (Part 1) subjects will receive double-blind therapy according to their randomized regimen (ORMD-0801 8 mg or 16 mg, or excipient matched placebo) to be taken QHS or BID. Subjects will then enter Part 2 at the same dose and regimen administered in Part 1. **Part 2:** During Part 2, subjects will remain on fixed doses of ORMD-0801 (or placebo) for 10 weeks. Doses will not be adjusted unless clinically indicated for adverse events or hypoglycemia. Overall glycemia will be measured by A1C at baseline and over 12 weeks of treatment. Additional measures will include fasting plasma glucose (FPG) drawn at clinic visits, outpatient SMBG values and adverse events recorded in the diary. Subjects will undergo blinded continuous glucose monitoring (CGM) for 2 weeks at baseline (on at Visit 1, off at Visit 3) and end-of-study (on at Visit 8, off at Visit 9). Standardized Mixed Meal Tolerance Testing (MMTT) will be performed at baseline (Visit 3) and at end-of-study (Visit 9). A1C will also be measured at intervals. Throughout the 12-week treatment period, subjects will be monitored and may be considered for "rescue" in case of persistent symptomatic hyperglycemia (see Rescue Criteria) to restore adequate glycemic control.
Primary Endpoint	• Mean change in HbA1C from baseline to Week 12 (Visit 9, Part 2 Week 10) of the treatment period.
Secondary Endpoints	• Means and mean changes from baseline over time for HbA1C and FPG. • Change from baseline to Week 12 (Visit 9, Part 2 Week 10) in postprandial glucose (PPG) parameters during a MMTT, including $AUC_{0\text{-}60}$, $AUC_{0\text{-}120}$, and 1 & 2-hour PPG absolute levels and excursions. • Changes from baseline in glycemic parameters measured using outpatient CGM. • Change in weight from baseline to Week 12 (Visit 9, Part 2 Week 10) of the treatment period. • Proportion of subjects requiring glycemic rescue therapy during the treatment period. • Safety assessed by adverse event reporting including adverse events of special significance such as hypoglycemia.
Exploratory Endpoints	• Patient reported outcomes, by Diabetes Treatment Satisfaction $Questionnaire_{status}$ ($DTSQ_s$) and $Questionnaire_{change}$ (DTSQc) score over 12 weeks.
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

	begin a 2-week single-blind placebo run-in to evaluate compliance with the study procedures and assessment of baseline glycemic control. The double-blind active treatment phase will last a total of 12 weeks. A follow-up visit is required two weeks after the end of Part 2. The total length of participation is approximately 15-17 weeks depending on Screening time.
Subject Selection Criteria	**Inclusion** 1. Male and female subjects aged 18 and older. 2. Established diagnosis of T2DM for at least 6 months prior to Screening, with an HbA1C ≥ 7.5%. 3. Stable dose of metformin (at least 1500 mg or maximal tolerated dose)/oral antidiabetic (OAD) 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: SU, DPP-4, SGLT-2, or TZD. 5. Body mass index (BMI) up to 40 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. 8. Females who are are not of childbearing potential are defined as: a. post-menopausal (defined as at least 12 months with no menses in women ≥45 years of age) or b. has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to Screening 9. Subjects who are of childbearing potential must: a. agree to remain abstinent from heterosexual activity† or agree to use (or have their partner use) acceptable contraception to prevent pregnancy within the projected duration of the trial and for 14 days after the last dose of blinded investigational product. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include: i. Use of one of the following double-barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom ii. Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and

intramuscular agents, and cutaneous patch]) with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or IUD.

iii. Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above).

iv. Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).

[†]Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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: eGFR $\leq$ 30 ml/min/1.73 m^2 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 (other than treated atrial fibrillation), 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 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. One or more contraindications to metformin as per local label. 19. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption. 20. At the Principal Investigator's discretion, any condition or other factor that is deemed unsuitable for subject enrollment into the study.
Statistical Methods	The primary endpoint for this study is the change from baseline in HbA1C at Visit 9 (Part 2 Week 10).Mean change from baseline to Week 12 HbA1C (Visit 9 value – Visit 3 value) will be tested using an analysis of covariance (ANCOVA) model using baseline HbA1c and whether the subject is using additional antidiabetes drugs (beyond Metformin) as covariates.

	Observed means and mean changes from baseline for HbA1C and FPG will be analyzed by visit using a method similar to the primary endpoint. Change from baseline to Week 12 (Visit 9, Part 2 Week 10) in PPG parameters during a MMTT, including AUC_{0-60}, AUC_{0-120}, and 1 & 2-hour PPG absolute levels and excursions will be analyzed using a method similar to the primary endpoint. Changes from baseline to Week 12 (Visit 9, Part 2 Week 10) in mean 24-hour, mean day time (6 AM to 10 PM) and mean night time (10 PM to 6 AM) glucose as measured by CGM will be analyzed using a method similar to the primary endpoint. For a day to be included in the calculations of the overall means, the subject must have at least 80% of the expected glucose readings. Changes from baseline to Week 12 (Visit 9, Part 2 Week 10) in weight will be analyzed using a method similar to the primary endpoint except that there will be no imputation for missing values (only observed values will be analyzed). Proportion of subjects requiring glycemic rescue therapy during the treatment period will be summarized by frequency counts.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A1C	HbA1C (hemoglobin A1C)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CAN	cardiac autonomic neuropathy
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CHF	congestive heart failure
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DTSQs	Diabetes Treatment Satisfaction Questionnaire
DTSQc	Diabetes Treatment Satisfaction Questionnaire Change
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EW	early withdrawal
FBG	fasting blood glucose
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GLP-1	glucagon-like peptide 1
HbA1C	hemoglobin A1C
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 Harmonization
IND	Investigational New Drug application
IRB	Institutional Review Board
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed Meal Tolerance test
NYHA	New York Heart Association
OAD	oral antidiabetic
PPG	post-prandial glucose
SAE	serious adverse event
SBP	systolic blood pressure
SBTI	soybean trypsin inhibitor

SMBG	self-monitored blood glucose
SOP	standard operating procedure
T2DM	type 2 diabetes mellitus
TIA	transient ischemic attack
TEAE	treatment-emergent adverse event
TSH	serum thyrotropin
TZD	thiazolidinedione
WCBP	woman of childbearing potential
WHO	World Health Organization

1 INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder that has reached epidemic proportions in the United States, affecting almost 8% of the U.S. population in 2007, and worldwide (Centers for Disease Control and Prevention, 2008). Diabetes mellitus is defined by hyperglycemia (increased concentration of glucose in the blood) caused by defective insulin secretion (type 1), resistance to insulin action (type 2), or a combination of both. Diabetes mellitus leads to an increased risk of microvascular damage (retinopathy, nephropathy and neuropathy), reduced life expectancy, increased risk of macrovascular complications (ischemic heart disease, stroke, and peripheral vascular disease), and diminished quality of life. This illness requires continuing medical care and subject self-management and education to prevent acute complications and to reduce the risk of long-term complications (American Diabetes Association, 2009).

The World Health Organization (WHO) has established diagnosis criteria for type 2 diabetes mellitus (T2DM) of fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L), plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) at 2 hours following ingestion of 75 g anhydrous glucose in an oral glucose tolerance test, or random plasma glucose greater than 200 mg/dL (11.1 mmol/L) in a person with symptoms of diabetes (World Health Organization, 2006). The treatment goal for subjects with this disease is long-term glycemic control (over both fasting and non-fasting blood glucose levels), which has been demonstrated in both type 1 and type 2 subjects to reduce the morbidities associated with uncontrolled glycemic levels (Diabetes Control and Complications Trial Research Group, 1993; Cleary et al., 2006; UK Prospective Diabetes Study Group, 1998a & 1998b). Typical options for glycemic control in subjects with T2DM include lifestyle management (diet and exercise), exogenously administered insulin, insulin plus oral drugs such as metformin or sulfonylureas, and oral drugs alone. Glycemic control is measured by subject self-monitored blood glucose (SMBG), subject self-monitoring of interstitial glucose, and periodic blood tests for measurement of hemoglobin A1C (HbA1C; A1C). HbA1C levels reflect average glycemia over several months and therefore provide a surrogate for glycemic control (U.S. Food and Drug Administration, 2008). A consensus statement written by the American Diabetes Association and the European Association for the Study of Diabetes targets an HbA1C level of <7% as an objective for nonpregnant adults, who do not have complicating factors, for the prevention of micro- and macrovascular disease (Nathan et al., 2009).

In addition to lifestyle modification through diet and exercise, a number of treatments are available to treat hyperglycemia in diabetic subjects. The choice of antihyperglycemic agents is made between physicians and subjects based upon the agents' effectiveness in lowering glucose, other effects that can reduce long-term complications, safety, tolerability, ease of use, and expense. For example, metformin is widely prescribed as an initial therapy to improve glycemic control in subjects with T2DM. It decreases hepatic glucose output and lowers fasting glycemia, thereby reducing HbA1C levels. It is generally well-tolerated, with possible gastrointestinal adverse events and low incidence of hypoglycemia, but is contraindicated in subjects with renal dysfunction. Sulfonylureas lower glycemia by enhancing insulin secretion, and are effective in lowering HbA1C levels. Possible adverse events associated with this class of drugs include hypoglycemia (more frequent in elderly subjects) and weight gain. Other drugs such as thiazolidinediones (TZDs), glucagon-like peptide 1 (GLP-1) analogue, α-glucosidase inhibitors, glinides, and pramlintide are commercially available in the U.S., but are considered less well-

validated with respect to established use, efficacy, and cost-effectiveness for achieving target glycemic goals than lifestyle management, metformin, and sulfonylureas (Nathan et al., 2009).

Subcutaneously administered insulin is highly effective at lowering glycemia and helping subjects achieve target HbA1c levels. Insulin has no overall dose limit with respect to safety and provides an improved lipid profile. However, subcutaneously administered insulin requires daily injections and blood glucose monitoring, and is associated with weight gain and an increased risk of hypoglycemia. Insulin is available as formulations with different pharmacokinetic (PK) and pharmacodynamic (PD) profiles (e.g, rapid, regular, intermediate, or long acting, or mixtures of these). These different formulations are used (Nathan et al., 2006) to tailor appropriate insulin regimens on a per subject basis.

Oramed Ltd. is developing a proprietary oral formulation of recombinant human insulin (ORMD-0801). Oramed, located in Jerusalem, Israel, was established in 2006 and the company's proprietary platform technology is based on over 25 years of medical research at the Hadassah University Medical Center in Jerusalem, Israel.

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

The potential advantage of oral insulin in the treatment of elevated fasting blood glucose as compared to subcutaneously-administered insulin lies in its delivery to the hepatic portal vein. Orally-administered insulin, once transported across the gut wall, is ferried to the hepatic portal vein, mimicking the natural route of endogenous pancreatic insulin and delivering the insulin directly to the intended site of action. In contrast, subcutaneously-administered insulin reaches the liver through the systemic circulation thereby requiring higher systemic levels of insulin in order to achieve the same effect. Thus, oral insulin administration is expected to avoid systemic hyperinsulinemia and provide a reduced risk of hypoglycemia. The PK/PD profile of ORMD-0801 is well-suited to the control of both fasting blood glucose and subsequent pre-meal blood glucose levels due to the delayed onset of glucose lowering activity. Therefore, Oramed is pursuing oral administration of ORMD-0801 at bedtime and one or two other times during the day for the improvement of glycemic control in adult subjects with type 2 diabetes mellitus.

Oramed has completed five Phase 1 safety studies of various formulations of ORMD-0801 in healthy human volunteers. Four Phase 2 studies have been completed, two in subjects with type 2 diabetes, and two in subjects with type 1 diabetes. These Phase 2 studies investigated different formulations, the effect of meals at different times following ORMD-0801 administration, and the effect of ORMD-0801 on glucose as measured by continuous glucose monitoring over a ten day treatment period with three doses per day prior to meals. One Phase 2 study assessed the safety and effectiveness on fasting blood glucose of repeat bed time administration of ORMD-

0801 in subjects with type 2 diabetes over a period of six weeks. In ORA-D-007, the difference in mean HbA1C in the ORMD-0801 combined group vs. the placebo group was statistically significant and at all doses tested, ORMD-0801 was as well tolerated as placebo and was not associated with any serious AEs related to the drug. More recently, ORA-D-012 (Phase 2a) evaluated the effect of ORMD-0801 on glucose (continuous glucose monitoring) administered qd, bid, or tid and concluded that there was a benefit to dosing multiple times per day. These studies demonstrated that the drug product is well-tolerated and can effectively reduce plasma glucose levels. There were no significant safety observations and no serious adverse reactions were reported for the completed studies, although there were two self-reported events of hypoglycemia in the 6-week, Phase 2 study.

2 STUDY OBJECTIVES

2.1 Primary Objective

To compare the efficacy of ORMD-0801 to placebo in improving glycemic control in T2DM subjects inadequately controlled on oral therapy based on A1C.

2.2 Secondary Objective

To assess the safety of long-term, repeat administration of ORMD-0801 l in T2DM subjects inadequately controlled on oral therapy.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is designed to explore efficacy of ORMD-0801 when given in different regimens across a dose range for up to 12 weeks in subjects with T2DM. Approximately 360 subjects with type 2 diabetes will initially undergo a 2-week, single-blind placebo run-in period (Visits 1 and 3), followed by a 12-week treatment period (Visits 3 through 9). For Cohort A, the total 12-week treatment period will include a Part 1“dose escalation” interval (2 weeks) and a Part 2 stable dose “maintenance” interval (10 weeks, Visits 5 through 9). The stable dose interval will be sufficient to allow for a robust assessment of treatment effect based on the mean change from baseline in HbA1C (A1C). For Cohort B, the total 12-week treatment period will include a stable dosing period for both Part 1 (2 weeks, Visits 3 and 4) and Part 2 (10 weeks, Visits 5 through 9).

Single-Blind Placebo Run-in:
During the placebo run-in period subjects will self- administer blinded placebo study medication at night prior to bedtime (@ 10 PM ± 90 minutes each night, no sooner than 2 hours after dinner). Outpatient glycemic levels and adverse events will be measured using SMBG and recorded in a diary.

Treatment Period:
Cohort A:
Of the total 360 subjects, 265 subjects will be randomized to one of the following four treatment arms:

1) ORMD-0801 once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes)
2) ORMD-0801 twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast.
3) ORMD-0801 three times daily - TID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast and lunch.
4) Matched Placebo (either QHS, BID, or TID)

In addition, per FDA request, the remaining 20 subjects will receive excipient matched placebo in a non-randomized single-blind fashion, TID, according to the same schedule as described above.

Cohort B:

Of the total 360 subjects, 75 will be randomized to one of the following four treatment arms:

1) ORMD-0801 8 mg once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes).
2) ORMD-0801 8 mg twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast.
3) ORMD-0801 16 mg once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes).
4) ORMD-0801 16 mg twice daily - BID: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes) and 30-45 minutes prior to breakfast.
5) Excipient matched placebo once daily - QHS: dosed in the evening prior to bedtime (@ 10 PM ± 90 minutes)

Part 1:
Cohort A
In the first two weeks of active treatment (Part 1) subjects will receive double-blind therapy according to their randomized regimen (placebo or ORMD-0801) to be taken QHS, BID or TID. Subjects will undergo a step-wise dose escalation from a starting dose of 16 mg (Visit 3), to 24 mg (Visit 4), to a top dose of 32 mg (Visit 5 onward). Subjects will then enter Part 2.

Cohort B
In the first two weeks of active treatment (Part 1) subjects will receive double-blind therapy according to their randomized regimen (ORMD-0801 8 mg or 16 mg, or excipient matched placebo) to be taken QHS or BID. Subjects will then enter Part 2 at the same dose and regimen administered in Part 1.

Part 2:
During Part 2, subjects will remain on fixed doses of ORMD-0801 (or placebo) for 10 weeks. Doses will not be adjusted unless clinically indicated for adverse events or hypoglycemia. Overall glycemia will be measured by A1C at baseline and over 12 weeks of treatment.

Additional measures will include fasting plasma glucose (FPG) drawn at clinic visits, outpatient SMBG values and adverse events recorded in the diary. Subjects will undergo blinded

continuous glucose monitoring (CGM) for 2 weeks at baseline (on at Visit 1, off at Visit 3) and end-of-study (on at Visit 8, off at Visit 9). Standardized Mixed Meal Tolerance Testing (MMTT) will be performed at baseline (Visit 3) and at end-of-study (Visit 9). A1C will also be measured at intervals.

Throughout the 12-week treatment period, subjects will be monitored and may be considered for "rescue" in case of persistent symptomatic hyperglycemia (see Rescue Criteria) to restore adequate glycemic control.

3.2 Screening (1 to 3 Weeks prior to Visit 1)

At the Screening Visit, 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 11.1.4 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.

Screening activities after obtaining informed consent will be conducted and consist of the following:

- Completion of medical and social history, including tobacco, alcohol, caffeine, drug use, and disease history questionnaire;
- Collection of demographic data (sex, age, race/ethnicity);
- Review of prior and current medications and supplements;
- Review inclusion and exclusion criteria.
- Physical examination.
- 12-lead electrocardiogram (ECG).
- Measurement of height and weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG, A1C, C-peptide, immunogenicity testing, and serum thyrotropin/TSH), and urinalysis (see Section 6.1.5 for list of tests).
    - Urine drug screen.
    - Serum pregnancy test (women of childbearing potential/WCBP only).
- Remind subjects to arrive fasting for Visit 1.

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

- the use of adequate contraceptive methods (see Section 4.1) for the duration of the study (Screening through Follow-Up Visit 10);
- minimal use of concomitant medications during the study, if possible, and avoid prohibited medications as defined in Section 5.7;
- 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 of this protocol (note that this includes assessments through 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 Run-In

3.3.1 Visit 1 (Run-In Week 0)

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

- Review of prior and current medications and supplements;
- Review inclusion and exclusion criteria;
- Measurement of weight;
- Measurement of vital signs (SBP/DBP and heart rate);
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG and A1C), and urinalysis (see Section 6.1.5 for list of tests);
    - Urine pregnancy test (WCBP only);
- Perform DTSQs questionnaire.
- Provide subjects with SMBG, nutrition, and hypoglycemic symptom training.
- Provide subjects with e-diaries and instruct on how to use them to collect essential data.
- Subjects will be instructed on the proper placement and use of the CGM device and the device will be calibrated. NO ACETAMINOPHEN usage should occur during the CGM monitoring periods. Subjects should notify the study staff if they used acetaminophen (or

any acetaminophen containing products) during the CGM monitoring period. Subjects will also be provided a paper diary during the CGM period to ensure dose times and meal times are recorded.
- Provide subjects with SMBG meters and supplies (lancets and test strips) and instruct on how to use them. This will include instructions for collecting 7-Point SMBG one to two per week (within 5 days prior to their upcoming Visit), recording insulin doses, and bringing meter to every clinic visit.
- Dispense placebo with instructions for administration (Cohort A: one capsule from each bottle to be taken at bedtime @ 10 PM ± 90 minutes, each night no sooner than 2 hours after dinner; Cohort B: one capsule to be taken at bedtime @ 10 PM ± 90 minutes, each night no sooner than 2 hours after dinner).
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles
- Remind subjects to arrive fasting for Visit 2.

3.3.2 Visit 2 (Run-In Week 1 ± 3 days)

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

- Review of prior and current medications and supplements;
- Measurement of vital signs (SBP/DPB and heart rate);
- Collection of fasted blood sample for FPG.
- Urine pregnancy test (WCBP only);
- Remove CGM device and download the data.
- Insert new CGM sensor. Subjects will be instructed on the proper placement and use of the CGM device and the device will be calibrated. NO ACETAMINOPHEN usage should occur during the CGM monitoring periods. Subjects should notify the study staff if they used acetaminophen (or any acetaminophen containing products) during the CGM monitoring period. Subjects will also be provided a paper diary during the CGM period to ensure dose times and meal times are recorded.
- Review e-diary, paper diary, and SMBG data.
- Collect unused placebo and review e-diary for compliance.
- Review e-diary for hypoglycemic events and completeness of entries.
- Re-dispense placebo with a reminder on instructions for administration.
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles
- Remind subjects to arrive fasting for Visit 3.

3.4 Part 1

3.4.1 Visit 3 (Part 1 Week 0 ± 3 days)

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medications and the following procedures will be performed:

- Review of prior and current medications and supplements;

- Review inclusion and exclusion criteria;
- Physical examination;
- Measurement of weight;
- Measurement of vital signs (SBP/DPB and heart rate);
- Remove CGM device and download the data.
- Collect and review the paper diary for completeness of entries.
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG and A1C), and urinalysis (see Section 6.1.5 for list of tests);
    - Urine drug screen;
    - Urine pregnancy test (WCBP only);
- Perform MMTT test:
    - No therapy is given prior to the baseline MMTT test.
    - Collection of blood samples for insulin, glucose, and C-peptide analysis prior to the start of the MMTT test at -50 and – 5 minutes (See section 6.2.1).
    - Additional blood samples will be drawn at 60 and 120 minutes (±10 minutes) post-prandially to obtain insulin and glucose levels. The exact time of the blood draw, even if it falls outside of the defined window, is to be recorded on the eCRF.
    - Blood samples for C-peptide will also be drawn at 60 minutes.
- **Cohort A:** Subjects will be randomized to double-blind placebo or ORMD-0801 QHS, BID, or TID, which will begin at Visit 3.
    - Subjects randomized to placebo will be randomized to receive placebo QHS, BID, or TID and follow the same corresponding dosing schedule shown below for ORMD-0801.
    - Subjects randomized to ORMD-0801 QHS will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner).
    - Subjects randomized to ORMD-0801 BID will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner) and one dose 30-45 minutes prior to breakfast.
    - Subjects randomized to ORMD-0801 TID will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner), one dose 30-45 minutes prior to breakfast, and one dose 30-45 minutes prior to lunch.
- **Cohort B:** Subjects will be randomized to double-blind excipient matched placebo QHS, ORMD-0801 8 mg QHS, ORMD-0801 8 mg BID, ORMD-0801 16 mg QHS, or ORMD-0801 16 mg BID, which will begin at Visit 3.
    - Subjects randomized to ORMD-0801 8 mg QHS will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner).
    - Subjects randomized to ORMD-0801 8 mg BID will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner) and one dose 30-45 minutes prior to breakfast.
    - Subjects randomized to ORMD-0801 16 mg QHS will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner).

  - Subjects randomized to ORMD-0801 16 mg BID will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner) and one dose 30-45 minutes prior to breakfast.
  - Subjects randomized to excipient matched placebo QHS will be instructed to take one dose at bedtime (@ 10 PM ±90 minutes, each night no sooner than 2 hours after dinner).
- Subject training on medication dosing.
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused placebo and review e-diary for compliance.
- Provide subjects with SMBG, nutrition, and hypoglycemic symptom training.
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles.
- Remind subjects to arrive fasting for Visit 4.

3.4.2 Visit 4 (Part 1 Week 1 ± 3 days)

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

- Review of prior and current medications and supplements;
- Measurement of vital signs (SBP/DPB and heart rate);
- Collection of fasted blood sample for FPG
- Urine pregnancy test (WCBP only);
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused ORMD-0801 and review e-diary for compliance.
- Dispense placebo or ORMD-0801 according to the subject's randomized dosing regimen; subjects in Cohort A will have their dose titrated up to 24 mg/dose.
- Subject training on medication dosing.
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles
- Remind subjects to arrive fasting for Visit 5.

3.5 Part 2

3.5.1 Visit 5 (Part 2 Week 0 ± 3 days)

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

- Review of prior and current medications and supplements;
- Measurement of weight;
- Measurement of vital signs (SBP/DPB and heart rate);
- Collection of fasted blood and urine samples for:
  - Clinical safety labs, including hematology, serum chemistry (with FPG and A1C), and urinalysis (see Section 6.1.5 for list of tests);
  - Urine drug screen;
  - Urine pregnancy test (WCBP only);

- Dispense placebo or ORMD-0801 according to the subject's randomized dosing regimen; subjects in Cohort A will have their dose titrated up to 32 mg/dose.
- Subject training on medication dosing.
- Perform DTSQs questionnaire.
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused ORMD-0801 and review e-diary for compliance.
- Provide subjects with SMBG, nutrition, and hypoglycemic symptom training.
- Evaluate subjects for potential rescue according to rescue criteria (Section 3.7).
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles
- Remind subjects to arrive fasting for Visit 6.

3.5.2 Visit 6 (Part 2 Week 1 ± 3 days) and Visit 7 (Part 2 Week 4 ± 3 days)

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

- Review of prior and current medications and supplements.
- Measurement of vital signs (SBP/DPB and heart rate).
- Collection of fasted blood sample for FPG;
- Urine pregnancy test (WCBP only);
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused medication and review e-diary for compliance.
- Dispense double-blind study drug (active or placebo) at Visit 7.
- Subject training on medication dosing.
- Evaluate subjects for potential rescue according to rescue criteria (Section 3.7).
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles.
- Remind subjects to arrive fasting for their next Visit.

3.5.3 Visit 8 (Part 2 Week 8 ± 3 days)

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

- Review of prior and current medications and supplements;
- Measurement of weight;
- Measurement of vital signs (SBP/DPB and heart rate);
- Collection of fasted blood and urine samples for clinical safety labs, including hematology, serum chemistry (with FPG and A1C), and urinalysis (see Section 6.1.5 for list of tests)
- Urine pregnancy test (WCBP only);
- Perform DTSQs followed by the DTSQc questionnaire.
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused medication and review e-diary for compliance.

- Subjects will be instructed on the proper placement and use of the CGM device and the device will be calibrated. NO ACETAMINOPHEN usage should occur during the CGM monitoring periods. Subjects should notify the study staff if they used acetaminophen (or any acetaminophen containing products) during the CGM monitoring period. Subjects will be dispensed CGM supplies in order to replace the sensor after 1 week (Week 9). Subjects will also be provided a paper diary during the CGM period to ensure dose times and meal times are recorded.
- Dispense double-blind study drug (active or placebo).
- Subject training on medication dosing.
- Evaluate subjects for potential rescue according to rescue criteria (Section 3.7).
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles
- Remind subjects to arrive fasting for Visit 9.

3.5.4 Visit 9 (Part 2 Week 10 ± 7 days)

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

- Review of prior and current medications and supplements.
- Physical examination.
- 12-lead ECG.
- Measurement of weight.
- Measurement of vital signs (SBP/DPB and heart rate).
- Remove CGM device and download the data.
- Collect and review the paper diary for completeness of entries.
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG, A1C, and immunogenicity testing), and urinalysis (see Section 6.1.5 for list of tests).
    - Urine pregnancy test (WCBP only).
- Perform MMTT test (Section 6.2.1).
    - Administer double-blind Study medication dose (32 mg or placebo) if subject is in the BID or TID arm 45 minutes prior to MMTT test.
    - Collection of blood samples for insulin, glucose, and C-peptide analysis prior to the start of the MMTT test at -50 and -5 minutes.
    - Additional blood samples will be drawn at 60and 120 minutes (±10 minutes) post-prandially to obtain insulin and glucose levels.
    - Blood samples for C-peptide will also be drawn at 60 minutes (±10 minutes).
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events. Collect e-diary.
- Collect unused medication and review e-diary for compliance.
- Record adverse events.
- Remind subjects to arrive fasting for follow-up Visit 10.

3.6 Follow-Up

3.6.1 Visit 10 (Part 2 Week 12 ± 7 days)

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

- Review of prior and current medications and supplements.
- Physical examination.
- Measurement of weight.
- Measurement of vital signs (SBP/DPB and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG and A1C), and urinalysis (see Section 6.1.5 for list of tests).
    - Urine pregnancy test (WCBP only).
- Discharge from the study.

3.7 Rescue Visit (RV)

In this study, subjects who experience symptomatic and worsening hyperglycemia may qualify for "rescue" to additional approved glucose-lowering agents added onto their study medication regimen that would allow them to remain in the study and complete remaining visits. Addition of rescue medication would allow eligible subjects to remain in the study and contribute safety and exposure data. The treatment of data obtained after the rescue visit for purposes of statistical analysis will be detailed in the Statistical Analysis Plan.

At the Investigator's discretion, subjects may be eligible for rescue based on glycemic criteria (Reference FDA Guidance):

• FPG greater than 270 mg/dL (15 mmol/L) from baseline to Part 2 Week 4 (Visit 7)
• FPG greater than 240 mg/dL (13.3 mmol/L) from Part 2 Week 8 to Part 2 Week 10 (Visit 9)

defined as two qualifying measurements within 3 days once of which was taken at the clinic. Persistent hyperglycemia requiring urgent intervention (such as random FPG > 300 mg/dL on multiple occasions) or symptoms of worsening hyperglycemia, which may include polyuria, polydipsia or weight loss will also qualify subjects for rescue evaluation.

These subjects can be rescued from hyperglycemia by adding an approved glucose-lowering agent according to local established practice (for example a long-acting GLP-1 receptor agonist or other medication (with the exception of sulfonylureas) to their daily regimen. Rescue medication would be prescribed in addition to ORMD-0801, allowing the subject to complete the remaining scheduled study visits. Any subject undergoing "rescue" should undergo a Rescue Visit as below, ideally prior to starting additional glucose-lowering therapy (e.g. rescue medication):

Subjects will report to the clinic in the morning following a 10-hour fast prior to taking morning medications and the following procedures will be performed:

- Review of prior and current medications and supplements;
- Physical examination.
- 12-lead ECG.
- Measurement of weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with FPG, A1C, and immunogenicity testing), and urinalysis (see Section 6.1.5 for list of tests); *If the FBG value measured on the day of the Rescue Visit remains > 250 mg/dL, then no MMTT test will be performed.*
- Urine pregnancy test (WCBP only);
- Review e-diary for completeness of entries, SMBG data and hypoglycemic events.
- Collect unused ORMD-0801 and review e-diary for compliance.
- Perform MMTT test:
    - Administer study medication (ORMD-0801 32 mg or placebo) 45 minutes prior to MMTT test.
    - Collection of blood samples for insulin, glucose, and C-peptide analysis prior to the start of the MMTT test at -50 and – 5 minutes (Section 6.2.1).
    - Additional blood samples will be drawn at 60 and 120 minutes (±10 minutes) post-prandially to obtain insulin and glucose levels.
    - Blood samples for C-peptide will also be drawn at 60 minutes (±10 minutes).
- Perform DTSQs followed by DTSQc questionnaire.
- Subjects will continue to take their double-blind study medication plus the rescue medication and proceed to complete the remaining protocol visits.
- Record adverse events.
- Remind subjects to collect 7-Point SMBG profiles.
- Remind subjects to arrive fasting for their next Visit.

3.8 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 the Visit 9 procedures will be performed. In addition, subjects will perform the DTSQs and DTSQc questionnaires. Subjects will then be discharged from the study.

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

3.9 Schedule of Events

Table 1 below describes the daily schedule of events from Screening through Follow-Up Visit 10.

Table 1. Daily Schedule of Events from Screening through Follow-Up Visit

		Run-In		Part 1		Part 2					Rescue	Follow-Up
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**RV**	**10**
Week	**-3 to -1**	**0**	**1**	**0**	**1**	**0**	**1**	**4**	**8**	**10**	**Variable**	**12**
Informed Consent	X											
Inclusion/Exclusion	X	X		X								
Medical History/Disease History Questionnaire	X											
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X			X				.		X	X	X
12-lead ECG	X									X	X	
Height and Weight[1]	X	X		X		X			X	X	X	X
Vital Signs[2]	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology, Urinalysis	X	X		X		X			X	X	X	X
Urine Drug Screen	X			X		X						
Pregnancy Test[3]	X	X	X	X	X	X	X	X	X	X	X	X
C-peptide and TSH	X											
Fasting Blood Glucose	X	X	X	X	X	X	X	X	X	X	X	X
HbA1C	X	X		X		X			X	X	X	X
Immunogenicity Testing	X									X	X	X
Randomization[4]				X								
CGM On/Off (Dispense/Review paper diary)		On		Off					On	Off		

		Run-In		Part 1		Part 2					Rescue	Follow-Up
Visit	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**RV**	**10**
Week	**-3 to -1**	**0**	**1**	**0**	**1**	**0**	**1**	**4**	**8**	**10**	**Variable**	**12**
Mixed Meal Tolerance Test[5]				X						X	X	
Dispense e-diary and Train on Use		X										
SMBG/Nutrition/Hypoglycemia Symptom Training		X		X		X						
Review e-diary SMBG data			X	X	X	X	X	X	X	X	X	
Review e-diary and assess for hypoglycemic events			X	X	X	X	X	X	X	X	X	
Collect study medication and review e-diary for compliance			X	X	X	X	X	X	X	X	X	
Dispense SB placebo		X	X									
Dispense study medication (active or placebo)				X	X	X		X	X			
Subject Training/Insulin Dosing Review [6]				X	X	X	X	X	X	X	X	
Assess for Rescue or Termination[7]						X	X	X	X		X	
Collect e-diary										X		
DTSQs		X				X			X		X	
DTSQc									X		X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

Table 1 Footnotes

[1]Height will be measured at Screening only. Weight will be measured as indicated.
[2]Heart rate and blood pressure.
[3]Serum pregnancy test at Screening, urine pregnancy test at Visits 1-10 and at Rescue Visits.
[4] Randomization will occur at Visit 3. Subjects will be dispensed single-blind placebo to be taken QHS during the run-in period. At Visit 3, subjects will be dispensed ORMD-0801 or placebo to be administered according to their randomization schedule. For Cohort A, subjects randomized to ORMD-0801 will start their dose at 16 mg at Visit 3, increase to 24 mg at Visit 4, and increase to 32 mg at Visit 5.
[5] At Visit 3 subjects will undergo a 2-hour MMTT. A final MMTT will occur on the final study visit also 45 min after administration of double-blind study medication.
[6]At each visit as indicated, subjects will be reminded about insulin dosing instructions and symptoms of potential hypoglycemia.
[7]Review FPG data from both in-clinic measurements and SMBG measurements and A1C to determine if a subject qualifies for rescue therapy based on Investigator discretion and the criteria outlined in Section 3.7. Subjects eligible for rescue should undergo a Rescue Visit (Section 3.7).

4 STUDY SUBJECT SELECTION

4.1 Inclusion Criteria

Each subject must meet all of the following criteria to be eligible for the study:

1. Male and female subjects aged 18 and older.
2. Established diagnosis of T2DM for at least 6 months prior to Screening, with an HbA1C ≥ 7.5%.
3. Stable dose of metformin (at least 1500 mg or maximal tolerated dose)/oral antidiabetic (OAD) 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: SU, DPP-4, SGLT-2, or TZD.
5. Body mass index (BMI) of up to 40 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.
8. Females who are not of childbearing potential are defined as:
    a. post-menopausal (defined as at least 12 months with no menses in women ≥45 years of age) or
    b. has had a hysterectomy and/or bilateral oophorectomy, or had bilateral tubal ligation or occlusion at least 6 weeks prior to Screening
9. Subjects who are of childbearing potential must:
    a. agree to remain abstinent from heterosexual activity[†] or agree to use (or have their partner use) acceptable contraception to prevent pregnancy within the projected duration of the trial and for 14 days after the last dose of blinded investigational product. Two methods of contraception will be used to avoid pregnancy. Acceptable combinations of methods include:
        i. Use of one of the following double-barrier methods: diaphragm with spermicide and a condom; cervical cap and a condom; or a contraceptive sponge and condom
        ii. Use of hormonal contraception (any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent [including oral, subcutaneous, intrauterine and intramuscular agents, and cutaneous patch]) with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; vasectomy; or IUD.
        iii. Use of an IUD with one of the following: condom; diaphragm with spermicide; contraceptive sponge; vasectomy; or hormonal contraception (see above).
        iv. Vasectomy with one of the following: diaphragm with spermicide; cervical cap; contraceptive sponge; condom; IUD; or hormonal contraception (see above).

[†] Abstinence can be used as the sole method of contraception if it is in line with the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and

ethics committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

4.2 Exclusion Criteria

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

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: eGFR $\leq$ 30 ml/min/1.73 m^2
    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 (other than treated atrial fibrillation), 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

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. One or more contraindications to metformin as per local label.
19. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption.
20. 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 5.7) 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 7.3.1)
7. Subject meets one of the exclusion criteria during the study
8. Subject wishes to withdraw for any reason.
9. Sponsor elects to end the study, or the Investigational Site elects to end the study at their site.
10. Any other reason that in the judgment of the Investigator poses unacceptable risk to the subject.

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

Except in cases of emergency, the Investigator should consult with the Sponsor and the Medical Monitor before removing the subject from the study. In some circumstances, it may be necessary to temporarily interrupt treatment 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 (Section 4.3) after the start of study treatment administration, reasonable efforts should be made to have the subject return for the early withdrawal evaluations (Section 3.8). 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 Cohort A: 2 soft gel capsules per dose (1 may be placebo as needed for blinding)

Dosage form Cohort B: 1 soft gel capsule per dose (may be placebo as needed for blinding)

Strength: 8 mg insulin per capsule or 16 mg insulin per capsule

Description: API (recombinant human insulin USP), in Oramed's proprietary formulation [SBTI, disodium EDTA, fish oil, aerosil, and TWEEN 80] in capsules.

Placebo control:

Fish oil in capsules, identical in appearance to ORMD-0801

Exipient-matched placebo control:

SBTI, disodium EDTA, fish oil, aerosil, and TWEEN 80, identical in appearance to ORMD-0801

5.1.1 Packaging and Labeling

All study medication will be shipped in pre-prepared kits to be allocated to subjects by the IWRS based on study period, randomization and individual dose regimen achieved. Study medication will be distributed at each visit sufficient to cover the time between visits. The investigational site pharmacist or designee will be responsible for dispensing the appropriate treatment period study treatment based on the randomization schedule.

Shipments of study medication for the double-blinded treatment period will be received in blinded packages. Study medication will be dispensed to the site with instructions for when treatment can be administered and with a diary for recording administration of study medication. Medication containers and any unused capsules will be retained at the study site after the treatment phase of the trial is complete. Unused study medication will be returned to the manufacturer for destruction.

The treatment packages will be labeled with the following information:

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

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

5.1.2 Storage and Handling

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

5.2 Randomization

Of the total 360 subjects, 265 subjects will be randomized to Cohort A and receive ORMD-0801 or placebo in one of 3 treatment regimens: QHS, BID, or TID. The actual treatment (ORMD-0801 or placebo) will be double-blinded to the subjects, investigators, monitors, and staff members responsible for treating and evaluating subjects, but the treatment regimen will be unblinded.

Creation, maintenance, and communication of the randomization scheme will be managed by an interactive web-based response system (IWRS). Subjects will be randomized 1:1:1 to QHS, BID, or TID and 1:3 (placebo:ORMD-0801) within each of those regimens at Visit 3. Therefore the overall randomization will be 1:1:1:1 (all placebo dosing regimens combined: ORMD-0801 QHS: ORMD-0801 BID: ORMD-0801 TID). Randomization will be in block sizes of 12 (1:3;1:3;1:3 [placebo QHS: ORMD-0801 QHS; placebo BID: ORMD-0801 BID; placebo TID: ORMD-0801 TID]).

An additional 75 subjects will be randomized to Cohort B and receive one of 5 treatment regimens (1:1:1:1:1): excipient matched placebo QHS, ORMD-0801 8 mg QHS, ORMD-0801 8 mg BID, ORMD-0801 16 mg QHS, or ORMD-0801 16 mg BID. Randomization will be in block sizes of 5 (1:1:1:1:1 [excipient matched placebo QHS: ORMD-0801 8 mg QHS: ORMD-0801 8 mg BID: ORMD-0801 16 mg QHS: ORMD-0801 16 mg BID]).

The randomization will be centralized and stratified by a) Sulfonylurea usage and b) whether they are on metformin alone or metformin plus one or 2 additional oral antidiabetic drugs at Screening. This will help ensure balanced treatment distribution of the subjects across the strata.

The additional 20 subjects in Cohort A who will receive excipient-matched placebo will not be randomized.

5.3 Study Treatment Administration

5.3.1 Study Treatment Periods

5.3.1.1 Single-Blind Run-In Placebo Administration

During the placebo run-in period subjects will be instructed to administer study medication (Cohort A: 1 capsule from each bottle; Cohort B: 1 capsule) at night prior to bedtime (@ 10 PM ± 90 minutes each night no sooner than 2 hours after dinner). Subjects will be dispensed sufficient placebo to continue self-administration until they return for Visit 2. At Visit 2, unused placebo will be collected and compliance will be reviewed. Subjects will be re-dispensed the placebo to continue self-administration until they return for Visit 3, including instructions to continue daily administration at home at bedtime (@ 10 PM ± 90 minutes each night no sooner than 2 hours after dinner).

5.3.1.2 Double-Blind Treatment Administration

In Part 1 all subjects will receive double-blind placebo or ORMD-0801 according to their randomization schedule.

Subjects in Cohort A only will undergo a step-wise dose escalation during the first two weeks to reach the target dose. ORMD-0801 dosing will begin with 16 mg administered QHS, BID or TID for the first week then increase to 24 mg for the second week. Dosing at 32 mg will commence at the beginning of Visit 5 (Start of Part 2) and continue through until Visit 9.

Subjects in Cohort B will remain on their randomized dosing regimen throughout Part 1 and Part 2.

5.4 Dose Modifications

Dose modifications will be discouraged, however modifications in dose level are permitted to avoid hypoglycemia if necessary in Cohort A only. The IWR system will be used to modify allocation of study medication as required to accommodate any blinded dose adjustments. This may also apply to subjects who are rescued during Part 2 (for persistent hyperglycemia) as they will receive additional approved glucose lowering agents while continuing their blinded study medication regimen.

If any subject on active treatment or placebo experiences worsening hyperglycemia, they may be eligible for rescue (Section 3.7). Subjects requiring additional treatment not otherwise eligible for rescue will be considered for discontinuation and referral (Section 4.3).

5.5 Measuring Subject Compliance

Dosing compliance will be assessed through review of diary entries as well as a count of unused study medication at each clinic visit.

5.6 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.

5.7 Concomitant Medications and Supplements

All medications and supplements (other than study treatment) taken by the subject from Visit 1 through the Follow-up Visit 10 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 the Follow-Up Visit 10;
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, 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

5.8 Dietary Restrictions

Subjects will fast overnight for at least 8 hours (10 hours recommended) prior to Screening and prior to all subsequent study visits.

Excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) will not be allowed from Screening through the Follow-Up Visit 10. Excessive alcohol use or binge drinking will be discouraged during the study, and alcohol will be prohibited 72 hours prior to each visit).

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 and Height

Weight will be measured at visits indicated in Table 1. The subject will be clothed while being weighed, but should remove shoes, coats, jewelry and other accessories. Height will be measured at Screening only 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 in case of Rescue Visit 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. During the Follow-up Visit 10, an abbreviated physical exam will be performed to note any newly developed abnormalities.

6.1.4 12-Lead ECG

A 12-lead ECG will be performed at Screening and at Visit 9 or in case of a Rescue Visit or Early Withrdawal . 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. At the Investigator's discretion, an additional ECG may be performed at the end of treatment; however, it will be recorded in source documents as an unscheduled assessment.

6.1.5 Clinical Laboratory Tests

Blood and urine for clinical safety laboratory assessments will be collected and processed using standard procedures at indicated in Table 1. A central laboratory will perform all clinical laboratory tests.

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

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 WCBP at Screening. A urine pregnancy test will be performed for WCBP at Visits 1-10 and during Rescue Visits.

6.1.5.3 Immunogenicity Testing

Samples will be drawn to test for antibodies to insulin pre-dose at Screening, then at Visit 9 and in case of Early Withdrawal.

6.1.5.4 Additional Screening Bloodwork

In addition to the blood tests listed above, A1C, FPG, C-peptide, and TSH will be measured according to Table 1.

6.1.5.1 Drugs of Abuse

Drugs of abuse urine screens will be completed as indicated in Table 1, according to the laboratory manual provided by the central laboratory. These will include testing for amphetamines, barbiturates, cocaine metabolites, opiates, and benzodiazepines.

6.2 Efficacy Assessments

6.2.1 Mixed Meal Tolerance Test (MMTT)

All subjects will have mixed meal tolerance testing throughout the study. MMTT will be performed as indicated in Table 1. All subjects will report to the research center following a 10 hour fast prior to taking morning medications. All MMTT should be scheduled at the same time for each subject. *If the fasting blood glucose value measured on the day of the Rescue Visit remains > 250 mg/dL, then no MMTT test will be performed but an attempt will be made to reschedule.*

1) Baseline blood samples will be drawn at -50 minutes (±10 minutes) and at -5 minutes (±5 minutes) from the start of the meal. Blood samples will be drawn for insulin, glucose, and C-peptide levels.
2) 45 minutes prior to the start of the meal (time 0), subjects will receive their morning dose of study drug (active or placebo, depending on the Visit). Subjects' blood glucose (BG) must be >70 mg/dL and <250 mg/dL prior to initiating dosing.
3) At 0 time, the subject will receive a standardized meal, which should be ingested over 5 minutes.
4) Additional blood samples will be drawn at 60 and 120 minutes (± 10 minutes) after the start of the meal to obtain insulin and glucose levels. Samples for C-peptide will also be drawn at 60 minutes (± 10 minutes).

6.2.2 Self-Monitored Blood Glucose (SMBG)

Subjects will be asked to collect daily blood glucose measurements throughout the study using the supplied glucose meter. SMBG profiles must be obtained during any 1-2 days within 5 days of the next study visit. This means subjects could perform SMBG on 1-2 consecutive days (e.g. just prior

to their study visit) or on 1-2 non-consecutive days if they are completed within the 5 days immediately preceding a study visit.

SMBG profiles must be collected at specific times relative to outpatient dosing and meals. It is important for subjects to take the post-prandial fingerstick glucose measurement within this time.

It is important to remind subjects to record the times of dosing, the times of meals and the times of fingerstick blood glucose measures particularly during the dose escalation period.

- **7-Point Self-Monitored Blood Glucose Profiles**
  7-Point SMBG profiles should include self-glucose measurements in the morning (while fasting and just prior to taking study medication) and ~ 60 minutes (1 hour) after eating breakfast; again both prior to and 60 minutes after lunch and dinner. A final measurement should be taken prior to bedtime.

6.2.3 Continuous Glucose Monitoring

CGM Dexcom G4 devices will be provided at Visit 1 and Visit 8. Data will be collected for 2 weeks. Subjects will be taught how and when to calibrate the device during the collection period. Subjects must be instructed that NO ACETAMINOPHEN usage should occur during the CGM monitoring periods. Investigator should inquire and subjects should notify the study staff if they used acetaminophen (or any acetaminophen containing products) during the CGM monitoring period.

6.3 E-Diary

At Run-in Visit 1, eligible subjects will be given an e-diary and will be trained to enter specific data into the diary.

The diary will include sections for:

- SMBG values and time of day, subjects.
- Dosing time(s) for study drug (active or placebo) administration
- Time of day and type of meal (breakfast, lunch, dinner, and snacks)
- Information related to hypoglycemia: exact time and date of hypoglycemia; symptoms, if any; treatments, if any; and specific circumstances.
    - Subjects should record how the episode was resolved using the text input on the E-Diary and specifically record
        - Did they require assistance from someone else to resolve the hypoglycemia
            - This means that without the help of another person the subject would probably not have been able to help themselves including being able to obtain and self-administer glucose.
            - This would include the requirement for medical assistance or administration of glucagon

- Did they experience confusion, or changes in their ability to think and act (such as becoming irritable or aggressive and not understanding their condition?)

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

7 ADVERSE EVENTS AND SAFETY REPORTING

7.1 Safety and Tolerability Assessments

Safety and tolerability will be assessed on an ongoing basis by review of reported AEs, physical examinations, 12-lead ECGs, weight, vital signs (SBP/DBP and heart rate), 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 Adverse Events of Special Interest

7.3.1 Adverse Events of Hypoglycemia

Episodes consistent with hypoglycemia will be reported as adverse events of special interest. 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, including those that occur during clinic visits and those that are recorded in e-diaries, 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 as well as review of SMBG values with or without symptoms 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.

7.3.2 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. Protocol specified algorithms will allow subjects to receive additional rescue medication that may enable them to remain in the study (Section 3.7).

7.4 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.

7.5 Eliciting and Reporting of Adverse Events

AE monitoring will start immediately following the first dose of run-in placebo and will continue through the Follow-Up Visit. Any subject with a possible study treatment-related AE at the Follow-Up Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether 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 pretreatment and TEAEs, reported by the subject, observed or otherwise identified by the Investigator, or other Investigational Site personnel will be documented. Medical conditions existing at Screening should be recorded as medical history. New or worsening pre-existing medical conditions or diseases are considered AEs if they arise or worsen after the 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 through the Follow-Up Visit. Conditions leading to planned surgical procedures are not AEs if the condition(s) was (were) known before study treatment. In the latter case, the condition should be reported as medical history.

7.5.1 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 CRF 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 7.5.2 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 7.7);
- Assessment of the attributability of the AE to the study treatment [per definition in Section 7.5];
- Whether the event is expected (per definition in Section 7.8);
- 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 7.9).

7.5.2 Reporting of Serious Adverse Events, Including Death

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

SAEs, including death due to any cause, which occur during this study or within 30 days following the last dose of the study treatment, whether or not related to the administration of study treatment, must be reported by the Investigator or other Investigational Site personnel to the Medical Monitor by telephone or fax **within 24 hours of learning of the event**. 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: safety@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. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available. If the Medical Monitor is informed of a SAE via a telephone call, preliminary information will be obtained, and the study site will be instructed to fax an SAE Form.

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. An emergency code break envelope for each subject will be provided to the Investigational Site and also to the Medical Monitor. If the Investigational Site personnel need to unblind the study treatment and cannot access the relevant code break envelope at the site, they can contact the Medical Monitor.

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.

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.

7.6 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.

7.6.1 Potential Adverse Events Associated with ORMD-0801

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

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

7.7 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 2. 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 7.4.

7.8 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.

7.9 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.

7.10 Clinical Findings

Any significant clinical findings at the Follow-Up Visit will be followed until the condition returns to pre-study status, stabilizes, or can be explained as not being study treatment related. If the clinical finding is reported as an AE (per the criteria outlined in Section 7.5), 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-015. Additional details will be provided in the statistical analysis plan.

8.1 Study Design

The primary analysis is a comparison of change in HbA1c for the ORMD-0801 treated groups and placebo. Let pC be the delta HbA1C for the control (placebo) arm and let pT be the delta HbA1C for the treatment (ORMD-0801) arms. The primary analysis is:

$$H0 : pC=pT$$

$$H1 : pC<pT$$

Trial success is defined as rejecting the null hypothesis of no difference in delta HbA1C between active study drug and placebo.

In order to preserve on overall alpha level of 0.05, a stepwise approach will be used for hypothesis testing. The initial hypothesis will be ORMD-0801 TID versus combined placebo. If the initial hypothesis results in a rejection of H0, the secondary test , ORMD-0801 BID versus combined placebo, will take place. If both the initial and secondary hypotheses result in rejections of H0, the third test, ORMD-0801 QHS versus combined placebo will take place.

8.2 Sample Size

8.2.1 Cohort A

The primary efficacy endpoint is the change from baseline in HbA1C at Visit 9 (Part 2- Week 10) after 12 weeks of active treatment. Based on previous results, a drop in HbA1C of 0.6% is expected with a standard deviation of 1.2. The primary analysis is based on combining the BID and TID treatment regimens together to compare to combined placebo. In order to achieve 80% power, there 48 completers are needed per treatment group.

Assuming an approximate 20% drop out rate, 240 randomized subjects would yield around 192 completers or approximately 48 subjects per treatment group. This would provide 80% power to detect a decrease in HbA1C of 0.6% for the BID and TID active combined versus combined placebo.

An additional 20 non-randomized subjects will be enrolled to receive excipient matched placebo to ensure that the fish oil placebo does not have a significant effect on efficacy or safety. The choice of adding 20 subjects is not based on statistical considerations. .

8.2.2 Cohort B

For powering purposes, the combined Cohort B will be given the same weight as the primary dosing cohort (Cohort A). Thus, Cohort B will enroll 75 subjects to achieve 60 completers. Each of the 5 dosing groups within Cohort B will enroll 15 subjects each to achieve 12 completers.

8.3 Primary Efficacy Evaluation

The primary endpoint for this study is the change from baseline in HbA1C at Visit 9 (Part 2 Week 10). Randomization occurs at Visit 3 (Part 1 Week 0), during which subjects will be stratified by Screening HbA1C values and current treatment regimen.

8.3.1 HbA1C Evaluation

Mean change from baseline to Week 12 HbA1C (Visit 9 value – Visit 3 value) will be tested using an analysis of covariance (ANCOVA) model using baseline HbA1C and whether the subject is using additional antidiabetes drugs (beyond metformin) as covariates.

8.3.2 Handling of Missing or Spurious Data

The overall data will be analyzed using a multiple imputation method to account for missing or spurious data. Missing or spurious data will be imputed. Imputed values are drawn for a distribution (that can be different for each missing entry). This step results in *m* complete data sets. Each of the *m* completed data sets will be analyzed. This step results in *m* analyses. The results for the *m* analyses will be pooled into a final result. The details of how the missing or spurious values were imputed will be documented.

8.4 Secondary Efficacy Evaluation

Observed means and mean changes from baseline for HbA1C and FPG will be analyzed by visit using a method similar to the primary endpoint.

Change from baseline to Week 12 (Visit 9, Part 2 Week 10) in PPG parameters during a MMTT, including $AUC_{0\text{-}60}$, $AUC_{0\text{-}120}$, and 1 & 2-hour PPG absolute levels and excursions will be analyzed using a method similar to the primary endpoint.

Changes from baseline to Week 12 (Visit 9, Part 2 Week 10) in mean 24-hour, mean day time (6 AM to 10 PM) and mean night time (10 PM to 6 AM) glucose as measured by CGM will be analyzed using a method similar to the primary endpoint. For a day to be included in the calculations of the overall means, the subject must have at least 80% of the expected glucose readings.

Changes from baseline to Week 12 (Visit 9, Part 2 Week 10) in weight will be analyzed using a method similar to the primary endpoint except that there will be no imputation for missing values (only observed values will be analyzed).

Proportion of subjects requiring glycemic rescue therapy during the treatment period will be summarized by frequency counts.

8.5 Exploratory Efficacy Evaluation

Patient reported outcomes, by Diabetes Treatment Satisfaction $Questionnaire_{status}$ ($DTSQ_s$) and $Questionnaire_{change}$ (DTSQc) score over 12 weeks will be evaluated.

Excipient matched placebo will be compared to the fish oil placebo on the following endpoints:

- Change in HbA1c from baseline to Week 12
- Frequency of adverse events
- Frequency of hypoglycemic events.

8.6 Safety Evaluation

8.6.1 Safety Population

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

8.6.1.1 Safety Evaluation Part 1

Adverse events will be described as "Part 1 Emergent," defined as any AE that started (or worsened) after receiving the first dose of randomized treatment during Part 1 until the time of receiving the first dose of randomized treatment during Part 2 (or discontinuation from Part 1).

8.6.1.2 Safety Evaluation Part 2

Adverse events will be described as "Part 2 Emergent," defined as any AE that started (or worsened) after receiving the first dose of randomized treatment during Part 2.

8.6.2 Adverse Events

AEs will be coded using the most current version of MedDRA. The severity of AEs will be graded according to NCI CTCAE version 4.03.

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.

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

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

8.6.3 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. Shift tables from baseline (Visit 3) to postdose (Visit 6, Visit 8, Visit 9, and Visit 10) will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.6.4 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 (Visit 3) 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.

8.6.5 12-lead ECG

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

8.6.6 Physical Examination

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

8.6.7 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 taken within 30 days prior to the first dose of study treatment. The incidence of these prior and concomitant medications and supplements will be summarized.

8.6.8 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.

Clinical laboratory samples will be processed by CMB and the results will be sent electronically to Integrium. The clinical laboratory results will be 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 the square root plus 1 of the total population 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.

11.1 Protection of Human Subjects

11.1.1 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.

11.1.2 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.

11.1.3 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).

11.1.4 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.

11.2 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.

11.3 Electronic Data Capture

All data required by the study protocol will be recorded in the electronic database provided by the EDC vendor. 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.

11.4 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.

11.5 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.

11.6 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 CRFs must be completed by authorized Investigational Site personnel who have undergone electronic CRF 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 8 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.

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