# Clinical Study Protocol: ORA-D-017

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| **Study Title:** | A Phase 2 Randomized, Open Label Crossover Study to Compare ORMD-0801 Given Once Daily at Bedtime to ORMD-0801 given Three Times Daily (45-90 minutes before Meals) in Subjects with Type 1 Diabetes |
| **Protocol Number:** | ORA-D-017 |
| **Study Phase:** | Phase 2 |
| **Principal Investigator:** | Joel M. Neutel, M.D.<br>Orange County Research Center (OCRC)<br>14351 Myford Rd., Suite B, Tustin, CA 92780 |
| **Sponsor:** | Oramed Ltd.<br>Hi-Tech Park 2/4 Givat Ram<br>PO Box 39098<br>Jerusalem, 91390, Israel |
| **Name of Sponsor Signatory:** | Miriam Kidron, PhD<br>Chief Scientific Officer and Director<br>Oramed Ltd. |
| **Protocol Version:** | 1.0 |
| **Date of Version:** | August 25, 2019 |

# SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned has reviewed and approved Protocol No. ORA-D-017 for issuance:

M Kidron — Signature

29-AUG-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.

| <Name of Investigator and Site> | Signature | Date |
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# SYNOPSIS

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| **Title** | A Phase 2 Randomized Open Label Crossover Study to Compare ORMD-0801 Given Once Daily at Bedtime to ORMD-0801 given Three Times Daily (45-90 minutes before Meals) in Subjects with Type 1 Diabetes |
| **Indication** | Type 1 Diabetes |
| **Clinical Phase** | Phase 2 |
| **Investigational Medicinal Product (IMP)** | **Name of the IMP:** ORMD-0801<br>**Dose and dosage regimen:**<br>Treatment A: 24 mg (16 mg capsule + 8 mg capsule) Once Daily (QD) at bedtime<br>Treatment B: 8 mg (8 mg capsule) three times a day (TID) 45-90 minutes before meals<br>Placebo capsules will be administered to subjects for 10 day run-in period prior to Randomization (subjects will take one capsule daily at bedtime).<br>**Formulation:**<br>Coated soft gel capsule [SBTI], disodium EDTA, fish oil, aerosol, and Tween 80<br>**Mode of administration:**<br>Oral |
| **Primary Objectives** | 1. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID on exogenous basal and bolus insulin requirements in subjects with Type 1 Diabetes (T1D) on their regular diet over a 4-week period.<br>2. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID and associated adjustments of basal and bolus insulin on mean 24-hour glucose and parameters of glycemic variability as measured by a Continuous Glucose Monitor over a 10-day period in subjects with T1D |

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| **Secondary Objectives** | 1. To compare the change from baseline in number of hypoglycemic episodes in subjects treated with Oral Insulin dosed QD to Oral insulin Dosed TID in subjects with T1D<br>2. To compare the change from baseline in Plasma A1C levels in subjects with T1D treated with Oral Insulin dosed QD or Oral Insulin dosed TID.<br>3. To explore changes in glucodynamics between the different dosing regimens.<br>4. To evaluate the safety of Oral Insulin |
| **Total Sample Size** | Approximately 26 completers |
| **Sites** | 3 sites |
| **Study Design** | This study is a Phase 2 randomized, crossover study comparing ORMD-0801 given QD versus TID in subjects with T1D. Subjects with T1D will have a screening visit (Visit 1) during which they will be required to review and sign the informed consent form. Medical history and demographics will be collected. Vital signs will be measured, physical exam will be performed, and blood and urine samples will be collected for hematology/chemistry/urinalysis.<br><br>Eligible subjects will be scheduled to return to the clinic in 1 week (Visit 2). Subjects fulfilling all inclusion/exclusion criteria will have a CGM placed, provided with a diary, dispensed Placebo capsules and asked to return to the clinic in 10 Days (Visit 3, Day 1) for randomization. At Visit 3, data from CGM will be downloaded and diaries will be collected. Blood samples will be collected in fasting for chemistry and HbA1c. Subjects will be randomized to receive either ORMD-0801 24 mg given once daily at bedtime, or ORMD-0801 8 mg given three times a day, 45-90 minutes before meals. Subjects will be instructed to continue their normal diet, and to adjust their basal and bolus insulin in the normal fashion. Subjects will be instructed to return to the clinic 10 days before Visit 5 (Visit 4, Day 18). At Visit 4, compliance will be assessed, IMP and diary dispensed and the CGM will be placed. Subjects will be instructed to return to the clinic in 10 days for Visit 5 (Day 28). At Visit 5 a fasting blood sample for chemistry panel and HbA1C will be drawn and after the diary has been collected and the CGM monitor removed, they will be crossed over to the alternate treatment regimen. IMP will be dispensed, and the subject will be asked to return 10 days before Visit 7 for Visit 6 (Day 46). At Visit 6, compliance will be checked, IMP and diary will be dispensed and |

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| | the CGM will be placed. Subjects will be instructed to return in 10 days for Visit 7 (Day 56). At Visit 7 the CGM will be removed, compliance checked, the diary will be collected, and a blood sample will be drawn for a chemistry panel and HbA1C. A physical examination will be performed, and the subject will exit the study.<br><br>Subjects will be provided with diaries at Visits 2, 4 and 6, and will be asked to capture the amount of basal and bolus exogenous insulin administered each day and calculate their carbohydrate count for all meals and snacks over the 10-day CGM monitoring period. Diaries will be collected at Visits 3, 5 and 7. |
| **Study Endpoints** | Primary Endpoints:<br>1. To compare the amount of basal, bolus and total (basal + bolus) exogenous insulin utilized over the final 10 days of each treatment period.<br>2. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID and associated adjustments of basal and bolus insulin on mean 24-hour CGM glucose levels during the final 10 days of each treatment period.<br><br>Secondary Endpoints:<br>1. Glucodynamics over the final 10 days of each treatment period as measured by CGM:<br>a. Time in range 70 - 180 mg/dL<br>b. Time < 70 mg/dL<br>c. Time >180 mg/dL<br>d. Time >250 mg/dL<br>e. Glucose Coefficient of Variation<br>f. Low Blood Glucose Index (LBGI)<br>g. Glucose below 70 mg/dL Area Over the Curve ($AOC_{70}$)<br>2. Total daily non-oral insulin requirements in units per kilogram (kg) body weight over the last 10 days of each treatment period.<br><br>Exploratory Endpoints:<br>3. HbA1c measured at the end of each treatment period<br>4. Patient diary-reported carbohydrate intake over the final 10 days of each treatment period<br>5. Changes in body weight from baseline (Visit 2) to the end of each treatment period |

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| | 6. Other measures of hypoglycemia over the last 10 days of each treatment period:<br>a. Severe hypoglycemia (SH) events (impaired or loss of consciousness requiring assistance of another)<br>b. Documented symptomatic hypoglycemia (an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <70 mg/dl (3.9 mmol/L))<br>c. Total time <70 mg/dL by CGM<br>d. Nocturnal hypoglycemia, severe or documented symptomatic episodes (as defined above) occurring after the subject has retired for the primary sleeping period<br><br>Safety assessments evaluating:<br>• Changes in clinical laboratory tests (hematology, chemistry, urinalysis);<br>• Collection of adverse events (AEs);<br>• Changes in Vital sign measurements |
| **Duration of Participation** | Including screening period, subjects will participate in this study for about 77 days (11 weeks). |
| **Subject Selection Criteria** | **Inclusion Criteria**<br><br>Each subject must meet all of the following criteria to be eligible for study participation:<br><br>1. Male and female subjects aged 18 and older.<br>2. Body mass index (BMI) of 19-30 kg/m$^2$ at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening.<br>3. T1D subjects must have:<br>a. A documented history of type 1 diabetes for at least 6 months<br>b. Should be on an MDI regimen<br>c. C peptide levels of < 0.7 ng/mL<br>d. HbA1C ≥ 6.5% to ≤10%<br>4. Females of childbearing potential must have a negative serum pregnancy test result at Screening.<br>5. Females who are not of childbearing potential are defined as:<br>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

6. 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**

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| | Subjects who meet any of the following criteria must be excluded from the study:<br>1. Clinical diagnosis of type 2 diabetes;<br>2. Evidence of unawareness of hypoglycemia unawareness, a documented plasma glucose ≤50 mg/dL in the absence of symptoms of hypoglycemia at Screening.<br>3. FPG >300 mg/dL at Screening; a single repeat test is allowable.<br>4. Use of the following medications:<br>a. Administration of thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to Screening.<br>b. 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.<br>5. Laboratory abnormalities at Screening including:<br>a. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or >1.5X the upper limit of normal<br>b. Elevated liver enzymes (alanine transaminase (ALT), alanine aminotransferase (AST), alkaline phosphatase) >2X the upper limit of normal.<br>c. Very high triglyceride levels (>600 mg/dL); a single repeat test is allowable.<br>d. Any relevant abnormality that would interfere with the efficacy or the safety assessments during study treatment administration.<br>6. Subject has a Screening systolic blood pressure ≥165 mmHg or diastolic blood pressure ≥100 mmHg. Subjects will be allowed to take a BP rescue medication.<br>7. Any clinically significant ECG abnormality at Screening or cardiovascular disease. Clinically significant cardiovascular disease will include:<br>a. History of stroke, transient ischemic attack, or myocardial infarction within 6 months prior to Screening,<br>8. History of or currently have New York Heart Associate Class II-IV heart failure prior to Screening.<br>9. Presence of any clinically significant endocrine disease according to the Investigator (euthyroid subjects on replacement |

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| | therapy will be included if the dosage of thyroxine is stable for at least six weeks prior to Screening).<br>10. Presence of any clinically significant condition (in the opinion of the Investigator) that might interfere with the evaluation of study medication, such as significant renal, hepatic, gastrointestinal (GI), cardiovascular (CV), immune disease, blood dyscrasias or any disorders causing hemolysis or unstable red blood cells, or clinically important hematological disorders (i.e. aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia) at Screening.<br>11. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption.<br>12. Presence or history of cancer within the past 5 years of Screening, with the exception of adequately-treated localized basal cell skin cancer or in situ uterine cervical cancer.<br>a. A subject with a history of malignancy >5 years prior to Screening should have no evidence of residual or recurrent disease.<br>b. A subject with a history of melanoma, leukemia, lymphoma, or renal carcinoma is excluded.<br>13. 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.<br>14. Positive history of HIV.<br>15. Known allergy to soy.<br>16. 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. Subjects who have had bariatric surgery are also excluded.<br>17. Subject is pregnant or breast-feeding.<br>18. 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.<br>19. At the Principal Investigator's discretion, any condition or other factor that is deemed unsuitable for subject enrollment into the study. |

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| **Statistical Methods** | Subjects will be analyzed under 3 treatment regimens: Standard of Care (Baseline), Once a Day Dosing (QD) and Three Times a Day Dosing (TID).<br><br>Information collected in the daily diaries or via the Continuous Glucose Monitor (CGM) on the final 10 days of treatment will be analyzed using a Repeated Measures Analysis of Covariance with subject as a random effect with each of the 10 days being a single measure. When analyzing the exogenous insulin variables, CGM parameters (mean 24 hour glucose value and 24 hour time within 70-180 mg/dL range) and patient reported carbohydrate intake will be included as covariates. When analyzing CGM parameters, exogenous insulin (basal and bolus insulin amounts) and patient reported carbohydrate intake will be included as covariates. Treatment least squares means and change from baseline estimates will be derived using this linear model.<br><br>Information collected at the day 28 visits will be analyzed using an Analysis of Covariance model with subject as a random effect. Treatment least squares means and change from baseline estimates will be derived using this linear model. |

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
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| AE | adverse event |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BUN | blood urea nitrogen |
| CFR | Code of Federal Regulations |
| CGM | Continuous glucose monitoring |
| CRO | contract research organization |
| CRU | clinical research unit |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DBP | diastolic blood pressure |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EDTA | ethylenediaminetetraacetic acid |
| EW | early withdrawal |
| FDA | Food and Drug Administration |
| FPG | fasting plasma glucose |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyltransferase |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide 1 |
| HbA1c | hemoglobin A1c |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| HIV | Human Immunodeficiency Virus |
| HR | heart rate |
| IB | Investigator's Brochure |

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| ICF | informed consent form |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug application |
| IRB | Institutional Review Board |
| IUD | intrauterine device |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PD | Pharmacodynamic |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| SAE | serious adverse event |
| SBP | systolic blood pressure |
| SBTI | soybean trypsin inhibitor |
| SOP | standard operating procedure |
| T1D | Type 1 diabetes |
| TEAE | treatment-emergent adverse event |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |
| 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 (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, T1D), resistance to insulin action (Type 2, T2DM), 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, subject self-management, and education to prevent acute complications and reduce the risk of long-term complications (American Diabetes Association, 2009).

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

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

Subcutaneously administered insulin is highly effective at lowering glycemia and helping subjects achieve target HbA1c levels. Insulin has no overall dose limit with respect to safety (except for hypoglycemia) 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 to tailor appropriate insulin regimens on a per subject basis (Nathan et al., 2006).

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

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

Oramed has completed five Phase 1 safety studies of various formulations of ORMD-0801 in healthy human volunteers. Four Phase 2 studies have been completed, two in patients with T2DM, and two in patients with T1D. 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 (CGM) over a ten-day treatment period with three doses per day prior to meals. Notably, one Phase 2 study assessed the safety and effectiveness on fasting blood glucose of repeat bed time administration of ORMD-0801 in patients with T2DM over a period of 6 weeks. A Phase 1/2 dose-response study was also conducted. These studies demonstrated that the drug product is well-tolerated and can effectively reduce plasma glucose and C-peptide 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 six-week, Phase 2 study.

Oramed intends to continue the clinical development of ORMD-0801.

# 2 STUDY OBJECTIVES AND ENDPOINTS

## 2.1 Objectives

2.1.1 Primary Objective

1. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID on exogenous basal and bolus insulin requirements in subjects with Type 1 Diabetes (T1D) during the last 10 days of each treatment period.

2. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID and associated adjustments of basal and bolus insulin on mean 24-hour glucose and parameters of glycemic variability as measured by a Continuous Glucose Monitor over the last 10 days of each treatment period.

2.1.2 Secondary Objectives

1. To compare the change from baseline in number of hypoglycemic episodes in subjects treated with Oral Insulin dosed QD to Oral insulin Dosed TID in subjects with T1D over the last 10 days of each treatment period
2. To compare the change from baseline in HbA1C levels in subjects with T1D treated with Oral Insulin dosed QD or Oral Insulin dosed TID as measured at the end of each treatment period.
3. To explore differences in glucodynamics between the different dosing regimens during the last 10 days of each treatment period.
4. To evaluate the safety of Oral Insulin through the recording of adverse events, clinical laboratory test results (hematology, chemistry and urinalysis) and vital signs.

## 2.2 Endpoints

Primary Endpoints

1. To compare the amount of basal, bolus and total (basal + bolus) exogenous insulin utilized over the final 10 days of each treatment period.
2. To compare the impact of Oral Insulin dosed QD to Oral Insulin dosed TID and associated adjustments of basal and bolus insulin on mean 24-hour CGM glucose levels during the final 10 days of each treatment period.

Secondary Endpoints

3. Glucodynamics over the final 10 days of each treatment period as measured by CGM:
    a. Time in range 70 - 180 mg/dL
    b. Time <70 mg/dL
    c. Time >180 mg/dL
    d. Time >250 mg/dL
    e. Glucose Coefficient of Variation
    f. Low Blood Glucose Index (LBGI)

g. Glucose below 70 mg/dL Area Over the Curve ($AOC_{70}$)

4. Total daily non-oral insulin requirements in units per kilogram (kg) body weight over the last 10 days of each treatment period.

Exploratory Endpoints:

5. HbA1c measured at the end of each treatment period
6. Patient dairy-reported carbohydrate intake over the final 10 days of each treatment period
7. Changes in body weight from baseline (Visit 2) to the end of each treatment period
8. Other measures of hypoglycemia:
    a. Severe hypoglycemia (SH) events (impaired or loss of consciousness requiring assistance of another)
    b. Documented symptomatic hypoglycemia (an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration <70 mg/dl (3.9 mmol/L))
    c. Total time <70 mg/dL by CGM
    d. Nocturnal hypoglycemia, severe or documented symptomatic episodes (as defined above) occurring after the subject has retired for the primary sleeping period

Safety assessments evaluating:

- Changes in clinical laboratory tests (hematology, chemistry, urinalysis);
- Collection of adverse events (AEs);
- Changes in Vital signs measurements

# 3 INVESTIGATIONAL PLAN

## 3.1 Overall Study Design and Plan

This study is designed to compare ORMD-0801 given QD versus TID in subjects with T1D. The study will consist of seven visits (including Screening Visit).

During Screening, subjects will be required to sign the informed consent form. Medical and medication history and demographic information will be collected. Eligibility for participation will be evaluated. Vital signs (height, weight, seated SBP/DBP, and heart rate) will be measured, physical examination will be performed, and a blood and urine sample will be collected for hematology/chemistry/urinalysis.

Eligible subjects will be scheduled to return to the clinic in 1 week (Visit 2). Subjects fulfilling all inclusion/exclusion criteria will have a CGM placed, provided with a diary, dispensed placebo capsules and asked to return to the clinic in 10 days (Visit 3, Day 1) for randomization. At Visit 3, data from CGM will be downloaded and diaries will be collected. Blood samples

will be collected in fasting for chemistry and HbA1C. Subjects will be randomized to receive either ORMD-0801 24 mg given once daily at bedtime, or ORMD-0801 8 mg given three times a day, 45-90 minutes before meals. Subjects will be instructed to continue their normal diet, and to adjust their basal and bolus insulin in the normal fashion. Subjects will be instructed to return to the clinic in 10 days before Visit 5 (Visit 4, Day 18). At Visit 4, compliance will be assessed, IMP and diary dispensed and the CGM will be placed. Subjects will be instructed to return to the clinic in 10 days for Visit 5 (Day 28). At Visit 5 a blood sample for chemistry panel and HbA1C will be drawn, the diary collected, the CGM removed and the patient will be crossed over to the alternate treatment regimen. IMP will be dispensed, and the subject will be asked to return in 10 days before Visit 7 for Visit 6 (Day 46). At Visit 6, compliance will be checked, IMP and a diary will be dispensed and the CGM will be placed. Subjects will be instructed to return in 10 days for Visit 7 (Day 56). At Visit 7 the CGM will be removed, the diary will be collected, compliance checked, blood sample will be drawn for a chemistry panel and HbA1C. A physical examination will be performed, and the subject will exit the study.

Subjects will be provided with diaries at Visits 2, 4 and 6, and will be asked to capture the amount of basal and bolus exogenous insulin administered each day and calculate their carbohydrate count for all meals and snacks over the 10-day CGM monitoring period of each treatment period.

## 3.2 Screening (-21 Days prior to Randomization)

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 ICF (refer to Section 11.2.4 for further details regarding the ICF). The investigational site personnel obtaining written consent from the subject will also sign the consent form.

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 history (including start date for T1DM),
- Collection of demographic data (sex, age, race/ethnicity);

- Review of prior and current medications and supplements;
- Review inclusion and exclusion criteria.
- Physical examination.
- Measurement of height and weight.
- Measurement of vital signs (SBP/DBP and heart rate).
- 12-lead electrocardiogram (ECG).
- Collection of fasted blood and urine samples for:
    - Clinical safety labs, including hematology, serum chemistry (with fasting plasma glucose/FPG, HbA1c, C-peptide, and serum thyrotropin/TSH, FSH to confirm postmenopausal status in women, and urinalysis (see Section 6.3.5 for list of tests);
    - Infectious serology (HIV, HBV, HCV);
    - Serum pregnancy Test for women of childbearing potential

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

- Use of adequate contraceptive methods (see Section 4.1) for the duration of the study (Screening through Visit 7);
- 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 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 . 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 failure (including, where applicable, the unmet inclusion or exclusion 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 Visit 2 (Day -10 ± 2 days)

Subjects will report to the CRU in the morning. The following procedures will be performed:

- Review of medical history;
- Review of medications and supplements;
- Review inclusion and exclusion criteria;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Subjects will be fitted with the CGM device and data recording will begin;
- Dispensing of Run-in Placebo capsules
- Dispensing of diaries;
- Subjects will be reminded to fast for a minimum of 10 hours prior to arrival on Visit 3 (Day 1 ± 2 days).

## 3.4 Visit 3 (Day 1 ± 2 days)

Subjects will report to the CRU in the morning in fasting state. The following procedures will be performed:

- Collect data from CGM monitor;
- Review of medications and supplements;
- Collect and review diary;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Urine pregnancy Test for women of childbearing potential
- Collect fasting blood samples for serum chemistry (with fasting plasma glucose/FPG) and HbA1c;
- Review inclusion and exclusion criteria.
- Randomization of subjects to their individual study treatment sequence;
- Dispensing of IMP and instructions on use of IMP.
- Adverse events will be monitored and recorded.

## 3.5 Visit 4 (Day 18 ± 2 days)

Subjects will report to the CRU in the morning. The following procedures will be performed:

- Adverse events will be monitored and recorded;
- Review of medications and supplements;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Subjects will be fitted with the CGM device and data recording will begin;

- Dispensing of diaries;
- Re-dispensing of IMP;
- Assessment of compliance to IMP;
- Subjects will be reminded to fast for a minimum of 10 hours prior to arrival on Visit 5 (Day 28 ± 2 days).

## 3.6 Visit 5 (Day 28 ± 2 days)

Subjects will report to the CRU in the morning in fasting condition. The following procedures will be performed:

- Collect data from CGM monitor;
- Review of medications and supplements;
- Collect and review diary;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Urine pregnancy Test for women of childbearing potential
- Collect fasting blood samples for serum chemistry (with fasting plasma glucose/FPG) and HbA1c;
- Assessment of compliance to IMP;
- Crossover of study treatment;
- Dispensing of IMP;
- Adverse events will be monitored and recorded.

## 3.7 Visit 6 (Day 46 ± 2 days)

Subjects will report to the CRU in the morning. The following procedures will be performed:

- Review of medications and supplements;
- Adverse events will be monitored and recorded;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Subjects will be fitted with the CGM device and data recording will begin;
- Dispensing of diaries;
- Re-dispensing of IMP;
- Assessment of compliance with IMP;
- Subjects will be reminded to fast for a minimum of 10 hours prior to arrival on Visit 7

(Day 56 ± 2 days)

## 3.8 Visit 7 (Day 56 ± 2 days)

Subjects will report to the CRU in the morning in fasting condition. The following procedures will be performed:

- Review of medications and supplements;
- Collect data from CGM monitor;
- Collect and review diary;
- Measurement of vital signs (weight, seated SBP/DBP, and heart rate);
- Physical examination;
- Collect fasting blood samples for hematology, serum chemistry (with fasting plasma glucose/FPG), HbA1c and urinalysis;
- Returning of IMP;
- Assessment of compliance to IMP;
- Adverse events will be monitored and recorded.
- Discharge from the study.

Any subject with a possible study treatment related AE at Visit 7 will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related to study treatment that occurs within 14 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 electronic case report form (eCRF).

## 3.9 Early Withdrawal (EW)

If a randomized subject is withdrawn from the study prior to completing study treatment, the subject will be discharged from the study after following procedures will be performed:

- Review of medications and supplements;
- Vital signs (including weight, seated SBP/DBP, and heart rate);
- Physical examination;
- Collect data from CGM monitor (if applicable);
- Collect and review diary (if applicable);
- Collection of fasted blood and urine samples for:

- Clinical safety labs, including hematology, serum chemistry (with fasting plasma glucose/FPG), HbA1c and urinalysis (see Section 6.3.5 for list of tests).

- Returning of IMP;
- Assessment of compliance to IMP;
- Adverse events will be monitored and recorded;
- Discharge 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.

## 3.10 Schedule of Events

Table 1 below describes the daily schedule of events from Screening Visit 1 through Visit 7.

## Table 1. Daily Schedule of Events from Screening Through Visit 7

| Visit | Screening Visit 1 | Visit 2 | Randomization Visit 3 | Visit 4 | Visit 5 | Visit 6 | Visit 7 | EW |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-21** | **-10** | **1** | **18** | **28** | **46** | **56** | |
| **Window days** | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | ± 2 | |
| **Informed Consent** | X | | | | | | | |
| **Medical History** | X | X | | | | | | |
| **Demographics** | X | | | | | | | |
| **Concomitant Medications** | X | X | X | X | X | X | X | X |
| **Inclusion/Exclusion Criteria** | X | X | X | | | | | |
| **Physical Exam** | X | | | | | | X | X |
| **ECG** | X | | | | | | | |
| **Vital Signs**[1] | X | X | X | X | X | X | X | X |
| **Serum Pregnancy Test** | X | | | | | | | |
| **Urine Pregnancy Test** | | | X | | X | | | |
| **Infectious Serology** (HIV, HBV, HCV) | X | | | | | | | |
| **C-peptide, TSH, FSH** | X | | | | | | | |
| **Hematology** | X | | | | | | X | X |
| **Serum Chemistry** (with FPG) | X | | X | | X | | X | X |
| **HbA1c** | X | | X | | X | | X | X |
| **Urinalysis** | X | | | | | | X | X |
| **Randomization** | | | X | | | | | |
| **Treatment Crossover** | | | | | X | | | |
| **Treatment Compliance** | | | X | X | X | X | X | X |
| **Treatment dispensing/returning** | | X | X | X | X | X | X | X |
| **CGM Monitoring**[2] | | X | X | X | X | X | X | X |
| **Diary dispensing/collecting**[3] | | X | X | X | X | X | X | X |
| **Adverse Events** | | | X | X | X | X | X | X |
| **Study Disposition** | | | | | | | X | X |

## Table 1 Footnotes

[1]Vital signs include height, weight, heart rate, SBP, and DBP. Height will be measured at Screening only, without shoes.
[2]CGM monitor applied at Visits 2, 4, and 6; removed and downloaded at visits 3, 5, and 7 (or EW if applicable).
[3]Diary dispensed at Visits 2, 4, and 6; collected and reviewed at visits 3, 5, and 7 (or EW if applicable).

# 4 STUDY SUBJECT SELECTION

## 4.1 Inclusion Criteria

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

1. Male and female (non-childbearing potential) subjects aged 18 and older.
2. Body mass index (BMI) of 19-30 kg/m$^2$ at Screening and stable weight, with no more than 5 kg gain or loss in the 3 months prior to Screening.
3. T1D subjects must have:
    a. A documented history of type 1 diabetes for at least 6 months
    b. Should be on an MDI regimen
    c. C peptide levels of < 0.7 ng/mL
    d. HbA1C ≥ 6.5% to ≤10%
4. Females of childbearing potential must have a negative serum pregnancy test result at Screening.
5. 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
6. 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. Clinical diagnosis of type 2 diabetes;
2. Evidence of unawareness of hypoglycemia unawareness, a documented plasma glucose ≤50 mg/dL in the absence of symptoms of hypoglycemia at Screening.
3. FPG >300 mg/dL at Screening; a single repeat test is allowable.
4. Use of the following medications:
    a. Administration of thyroid preparations or thyroxine (except in subjects on stable replacement therapy) within 6 weeks prior to Screening.
    b. 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.
5. Laboratory abnormalities at Screening including:
    a. Abnormal serum thyrotropin (TSH) levels below the lower limit of normal or >1.5X the upper limit of normal
    b. Elevated liver enzymes (alanine transaminase (ALT), alanine aminotransferase (AST), alkaline phosphatase) >2X the upper limit of normal.
    c. Very high triglyceride levels (>600 mg/dL); a single repeat test is allowable.
    d. Any relevant abnormality that would interfere with the efficacy or the safety assessments during study treatment administration.
6. Subject has a Screening systolic blood pressure ≥165 mmHg or diastolic blood pressure ≥100 mmHg. Subjects will be allowed to take a BP rescue medication.
7. Any clinically significant ECG abnormality at Screening or cardiovascular disease. Clinically significant cardiovascular disease will include:
    a. History of stroke, transient ischemic attack, or myocardial infarction within 6 months prior to Screening,
8. History of or currently have New York Heart Associate Class II-IV heart failure prior to Screening.

9. Presence of any clinically significant endocrine disease according to the Investigator (euthyroid subjects on replacement therapy will be included if the dosage of thyroxine is stable for at least six weeks prior to Screening).
10. Presence of any clinically significant condition (in the opinion of the Investigator) that might interfere with the evaluation of study medication, such as significant renal, hepatic, gastrointestinal (GI), cardiovascular (CV), immune disease, blood dyscrasias or any disorders causing hemolysis or unstable red blood cells, or clinically important hematological disorders (i.e. aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia) at Screening.
11. History of gastrointestinal disorders (e.g. hypochlorhydria) with the potential to interfere with drug absorption.
12. Presence or history of cancer within the past 5 years of Screening, with the exception of adequately-treated localized basal cell skin cancer or in situ uterine cervical cancer.
    a. A subject with a history of malignancy >5 years prior to Screening should have no evidence of residual or recurrent disease.
    b. A subject with a history of melanoma, leukemia, lymphoma, or renal carcinoma is excluded.
13. 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.
14. Positive history of HIV.
15. Known allergy to soy.
16. 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. Subjects who have had bariatric surgery are also excluded.
17. Subject is pregnant or breast-feeding.
18. 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.
19. 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. The following are reasons to terminate a subject's participation in the study:

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.
    a. If a subject experiences hyperglycemia, defined in Section 7.3.2, blood glucose will be checked 1-2 hours later. If the glucose remains elevated, the subject will be withdrawn from 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. Subject wishes to withdraw for any reason.
7. Sponsor elects to end the study, or the Investigational Site elects to end the study at their site.
8. Any other reason that in the judgment of the Investigator poses unacceptable risk to the subject.

Reasons for study drug discontinuation may include the following:

1. Adverse event
2. Episodes of hypoglycemia as defined in Section 7.3.1.
3. Subject meets one of the exclusion criteria during the study
4. Any clinically significant change in the subject's medical condition

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. Subjects who discontinue study drug 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 CRF. 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 appointments/contacts, in order to ensure that he/she is in satisfactory health. If a subject withdraws from the study as a result of meeting discontinuation criteria after the start of study treatment administration, reasonable efforts should be made to have the subject return for the early withdrawal evaluations (Section 3.9). Any subject withdrawn due to a suspected study treatment -related AE should be followed until resolution or stabilization of the event.

Subjects may choose to withdraw authorization to use and disclose their PHI as defined by the HIPAA. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator prior to the date of such withdrawal will continue to be used and disclosed.

Randomized subjects who are discontinued from this study for any reason will not be replaced.

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

**Name of the IMP:** ORMD-0801
**Dose and dosage regimen:**

1. Treatment A: 24 mg (16 mg + 8 mg capsules) Once Daily (QD) at Bedtime
2. Treatment B: 8 mg (8 mg capsule) three times a day (TID) 45-90 minutes before meals
3. Placebo: Placebo capsules QD at bedtime during placebo run-in period 10 days prior to randomization.

**Formulation:** Coated soft gel capsule [SBTI], disodium EDTA, fish oil, aerosol, and Tween 80

**Mode of administration:** Oral

### 5.1.1 Packaging and Labeling

This study is an open label study. All study medication including Placebo will be shipped to site. The Investigational Site pharmacist will be responsible for dispensing the appropriate treatment based on the randomization schedule. Study medication will be dispensed to the site with instructions for treatment administration.

The treatment packages will be labeled with the following information:

- Study number
- Subject ID
- 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

.

### 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.

## 5.2 Randomization

This is a randomized, open label, crossover study. Approximately 26 eligible subjects with T1D will be randomized to all 2 treatment schedules.

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

## 5.3 Study Treatment Administration

All subjects will receive Placebo capsules once a day at bedtime during placebo run-in period for 10 days prior to randomization.

Subjects receiving Treatment A should take 16 mg + 8 mg capsules once a day at bedtime.

Subjects receiving Treatment B should take 8 mg capsule three times a day 45-90 minutes before meals.

## 5.4 Dose Modifications

This study does not include any planned dose modifications. Subjects will consume study treatment orally at the assigned (randomized) dose unless discontinuation criteria as defined in Section 4.3 are met.

## 5.5 Measuring Subject Compliance

Treatment compliance will be ascertained by accountability of returned IMP and recording in diary.

## 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 eCRF.

## 5.7 Concomitant Medications and Supplements

All medications and supplements (other than study treatment) taken by the subject from Visit 3/Day 1 through Visit 7 will be considered "concomitant" medications and supplements. Medications and supplements taken prior to Visit 3/Day 1 that are no longer being taken at the time of Visit 3/Day 1 will be considered "prior" medications and supplements.

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

The use of concomitant medications and supplements should be kept at a minimum, if possible. Any medications and supplements needed for the welfare of a subject and that in the judgment of the Investigator will not pose a significant risk to the subject for continued participation in the study or that will not interfere with the interpretation of the results of this study may be given to the subject. 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 within 30 days prior to Visit 3/Day 1 through Visit 7;
2. Any anti-diabetic drugs (except for those allowable by the inclusion criteria) including GLP-1 analogue, α-glucosidase inhibitors, glinides, and pramlintide within 6 weeks prior to Screening;
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 the subject.

## 5.8 Dietary Restrictions

Subjects will be advised not to make any drastic changes in their regular diet throughout the study. Excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) should

be avoided from Screening through Visit 7. Excessive alcohol use or binge drinking will be discouraged during the study.

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 Informed Consent

According to the ICH guideline for GCP (E6) and all institutional local, state, and federal laws, the Investigator will obtain and document informed consent for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol and Investigational Drug, its possible hazards, and their right to withdraw at any time, and will sign a form (ICF) indicating their consent to participate in the study prior to the initiation of study procedures. The subject's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated IRB and by Oramed Ltd. designee prior to its use. Refer to Section 11.2.4 for further details regarding informed consent.

## 6.2 Medical History and Prior Medications

At Screening, a complete medical history (including start date of T1DM) will be collected by subject interview. Medications and supplements, recent blood donations, illnesses, and participation in other Investigational Drug trials or clinical trials will also be recorded.

## 6.3 Safety Assessments

### 6.3.1 Weight and Height

Weight will be measured at visits as described in Table 1. Height will be measured at Screening only with the subject wearing no shoes.

### 6.3.2 Vital Signs

Vital signs (including seated SBP/DBP, and heart rate) will be recorded at visits as described in Table 1. Blood pressure and heart rate 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.

### 6.3.3 Physical Examination

A physical examination will be performed at visits as described in Table 1, or in case of Early Withdrawal. The physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological examination.

### 6.3.4 12-Lead ECG

A 12-lead ECG will be performed at Screening. 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.

### 6.3.5 Clinical Laboratory Tests

Blood and urine for clinical safety laboratory assessments will be collected and processed using standard procedures. 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.

#### 6.3.5.1 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
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (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

Pregnancy Test

#### 6.3.5.2 Follicle Stimulating Hormone Test

A serum FSH test will be performed in postmenopausal women.

#### 6.3.5.3 Additional Screening Bloodwork

In addition to the blood tests listed above, infectious serology (HIV, HCV, and HBV), FPG, $HbA_{1c}$, C-peptide, and TSH will be measured at Screening. FPG and $HbA_{1c}$ will be performed at visits as described in Table 1 and in case of Early Withdrawal.

### 6.3.6 Continuous Glucose Monitor (CGM)

CGM will be used to monitor subject glucose levels (including post-prandial) throughout the study. Further information about the device can be found in the laboratory manual.

Subjects will have the CGM implanted at visits as described in Table 1. The device will be removed and the data will be downloaded at each subsequent visit. Staff will be advised regarding appropriate procedures in the event of nocturnal hypoglycemia.

## 6.4 Review and Documentation of Medications and Supplements

All medications or supplements subjects are taking or have taken within 30 days prior to Visit 3/Day 1 through Visit 7 will be recorded in the subject's medical record and the medical history CRF.

All medications and supplements (other than study treatment) taken by the subject after Visit 3/Day 1 through Visit 7 assessments will be considered "concomitant" medications and supplements. Medications and supplements taken prior to Visit 3/Day 1 that are no longer being taken at Visit 3/Day 1 will be considered "prior" medications and supplements.

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 CRF.

# 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, vital signs (including weight, seated SBP/DBP, and heart rate), and clinical safety labs (hematology, serum chemistry, and urinalysis).

## 7.2 Definition of Adverse Event

An 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 (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

AEs with be collected starting with Visit 2/Day -10. However, AEs occurring between Visit 2/ Day -10 and Visit 3/Day 1 will be regarded as "pretreatment" if they occur before IP administration at Visit 3/Day 1. TEAEs are defined as any AE that starts or increases in severity after the first randomized dose of study IP on Visit 3/Day 1.

## 7.3 Definition of Serious Adverse Event

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

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

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject 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 at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

### 7.3.1 Adverse Events of Hypoglycemia

The CTCAE (version 4.0) definition for mild, moderate, and severe hypoglycemia based on blood glucose will be used, as shown below:

> Mild: from 55 to <70 mg/dL (3.0 to < 3.8 mmol/L)
>
> Moderate: from 40 to < 55 mg/dL (2.2 to < 3.0 mmol/L)

Severe: from 30 to < 40 mg/dL (1.7 to < 2.2 mmol/L)

Life Threatening: < 30 mg/dL (< 1.7 mmol/L)

Subjects with hypoglycemia will be provided with 2-4 glucose tablets as necessary until symptoms subside or blood glucose increases to greater than 70 mg/dL. If a patient has greater than 2 episodes of symptomatic hypoglycemia at any particular study visit, they will be terminated from the study.

### 7.3.2 Adverse Events of Hyperglycemia

Hyperglycemia will be defined as a blood glucose reading > 300 mg/dL. 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, the subject will be withdrawn from the study and treated according to the following criteria:

1. Subjects who are asymptomatic with a glucose reading >300 mg/dL and <500 mg/dL will be provided with dietary counseling and either adjustment of their current medication or addition of an alternative hypoglycemic agent.
2. Subjects who are symptomatic with a glucose reading >300 mg/dL and <500 mg/dL will be provided with dietary counseling, subcutaneous insulin on a sliding scale, and adjustment of their current medication or addition of an alternative hypoglycemic agent.
3. Subjects with a glucose reading ≥500 mg/dL will be provided with dietary counseling, subcutaneous insulin on a sliding scale, and adjustment of their current medication or addition of an alternative hypoglycemic agent.

## 7.4 Eliciting and Reporting of Adverse Events

AE monitoring will start immediately following the first dose study treatment and will continue through Visit 7. Any subject with a possible study treatment-related AE at Visit 6/Day 2 will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related to study treatment, that occurs within 14 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 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 Visit 7. Conditions leading to planned surgical procedures are not AEs if the condition(s) was (were) known before study treatment. In the latter case, the condition should be reported as medical history.

### 7.4.1 Routine Reporting of Adverse Events

All AEs, whether or not associated with the study treatment, that are observed by the Investigator, other Investigational Site personnel, or those reported by the subject will be recorded in the subject's source documentation and on the AE page of the eCRF. Copies of the SAE 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 7.4.2 for further detail) and regular regulatory reporting requirements under 21 CFR 312.33.

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

- Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);
- Date of onset of any new AE or worsening of a previously observed AE;
- Date of resolution of the event (or confirmation ongoing);
- Whether the event is serious (per definition in Section 7.3), and if so, the reason it is considered serious;
- Severity of AE (per definition in Section 7.6);
- Assessment of the attributability of the AE to the study treatment (per definition in Section 7.5);
- Whether the event is expected (per definition in Section 7.7);
- Action taken in treating the AE (including concomitant medications or therapies administered) and/or change in the study treatment administration or dose (including whether the study treatment was temporarily interrupted or discontinued);
- Outcome of AE (per definition in Section 7.8).

### 7.4.2 Reporting of Serious Adverse Events, Including Death

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

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 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.

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 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 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.

## 7.5 Causality Assessment of Adverse Events

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

### 7.5.1 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.

## 7.6 Adverse Event Severity Assessment

The severity of each AE will be graded according to the NCI CTCAE, version 4.03. The severity of AEs that are not specifically listed in the CTCAE will be categorized according to the general guidelines provided in the CTCAE, and as summarized in the table below.

**General Guidelines for Severity Assessment of Adverse Events**

| |
|---|
| **Grade 1**: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| **Grade 2**: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) [preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.]. |

| |
|---|
| **Grade 3**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden). |
| **Grade 4**: Life-threatening consequences; urgent intervention indicated. |
| **Grade 5**: Death related to AE. |

Note the distinction between the severity and the seriousness of an AE. A severe AE is not necessarily a SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above in Section 7.3.

## 7.7 Expectedness of Adverse Event

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

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

## 7.8 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Topic E2B, ICH Guideline.

- **Recovered/Resolved:** The subject has recovered fully from the AE without any remaining effects or impairment.
- **Recovered/Resolved with Sequelae**: The subject has recovered, but with an after effect possibly due to disease or treatment.
- **Not Recovered/Not Resolved:** The condition is still present.
- **Fatal:** Fatal should only be used when death is possibly related to the AE.
- **Unknown**: The primary outcome is not known at the time of the final assessment. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed until an outcome is known or followed up to the Final Study Visit. Any subject with a possible study treatment-related AE at the Final Study Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related to Study treatment (active or placebo), that occurs within 30 days following the last dose of Study treatment will be followed until resolution or stabilization of the event.

## 7.9 Clinical Findings

Any significant clinical findings 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 7.2), 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-017. Additional details will be provided in the statistical analysis plan.

## 8.1 Sample Size

An estimated total of 24 subjects are planned to be randomized to participate in the two dosing conditions in a randomized order. The study objectives (primary, secondary and exploratory) have not been previously explored, so there are no estimates of means or standard deviations to perform power calculations.

Safety will be a secondary endpoint for this trial and will be assessed primarily based on AEs. Secondary safety assessments will include physical examination, 12-lead ECG, vital signs (including weight, seated SBP/DBP, and heart rate), and clinical safety labs (hematology, serum chemistry, and urinalysis).

## 8.2 Statistical Considerations

Subjects will be analyzed under 3 treatment regimens: Standard of Care (Baseline), Once a Day Dosing (QD) and Three Times a Day Dosing (TID).

Information collected in the daily diaries or via the Continuous Glucose Monitor (CGM) on the final 10 days of treatment will be analyzed using a Repeated Measures Analysis of Covariance with subject as a random effect with each of the 10 days being a single measure. When analyzing the exogenous insulin variables, CGM parameters (mean 24 hour glucose value and 24 hour time within 70-180 mg/dL range) and patient reported carbohydrate intake will be included as covariates. When analyzing CGM parameters, exogenous insulin (basal and bolus insulin amounts) and patient reported carbohydrate intake will be included as covariates. Treatment least squares means and change from baseline estimates will be derived using this linear model.

Information collected at the day 28 visits will be analyzed using an Analysis of Covariance model with subject as a random effect. Treatment least squares means and change from baseline estimates will be derived using this linear model.

## 8.3 Basal, Bolus and Total Exogenous Insulin

The amount of basal, bolus and total exogenous insulin will be analyzed using the Repeated Measures Analysis of Covariance model indicated in Section 8.2. Least squares means, standard error and 95% confidence intervals will be presented for each treatment regimen and changes between treatment regimens.

Total daily non-oral insulin requirements in units per kilogram (kg) body weight will also be analyzed in a fashion similar to basal, bolus and total exogenous insulin.

## 8.4 Continuous Glucose Monitor Evaluation

For the purpose of analysis:

- 24-hour will be considered to be from 6AM to 6AM,
- Daytime will be considered to be from 6AM to 10PM,
- Nighttime will be considered to be from 10PM to 6AM, and

The area under the curve (AUC) will be derived for each of the time periods (24-hour, daytime and nighttime) for each of the 10 days for each treatment regimen. The average glucose measurement will be derived by dividing the AUC by the number of observed hours.

In addition to the mean values, the following CGM parameters will be derived:

- Time in range 70-180 mg/dL
- Time <70 mg/dL
- Time >180 mg/dL
- Time >250 mg/dL
- Glucose coefficient of variation
- Low blood glucose index (LBGI)
- Glucose below 70 mg/dL Area Over the Curve ($AOC_{70}$)

All of the CGM parameters will be analyzed for each of the time periods (24-hour, daytime and nighttime) using the Repeated Measures Analysis of Covariance Model indicated in Section 8.2.

## 8.5 Other Endpoints of Interest

HbA1c, average patient reported carbohydrate intake and body weight will be summarized using an Analysis of Covariance Model as indicated in Section 8.2.

## 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.

### 8.6.2 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. AEs with be collected starting with Visit 2/Day -10. However, AEs occurring between Visit 2/Day -10 and Visit 3/Day 1 will be regarded as "pretreatment" if they occur before IP administration at Visit 3/Day 1. TEAEs are defined as any AE that starts or increases in severity after the first randomized dose of study IP on Visit 3/Day 1.

The incidence of TEAEs will be tabulated by MedDRA preferred term, system organ class, treatment group, severity, and assigned relationship to study treatment. The incidence for each TEAE will be provided as the total number of subjects that experienced the TEAE, as well as the percentage of the population that this 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 treatment and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Individual change from baseline (Screening) in laboratory values will be calculated and summarized descriptively. A clinically significant change from baseline (Screening) 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 (Screening) in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from baseline (Screening) will be recorded as a TEAE if deemed appropriate by the Investigator.

### 8.6.5 12-lead ECG

Individual 12-lead ECG assessments at screening will be listed.

### 8.6.6 Physical Examination

Individual physical examination findings will be listed for each visit in which a physical examination occurred. A clinically significant change from baseline (Screening) 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.

All medications and supplements (other than study treatment) taken by the subject from Visit 2/Day 1 through the Visit 7 will be considered “concomitant” medications and supplements. Medications and supplements taken prior to the first dose of ORMD-0801 that are no longer being taken at the time of the first dose of ORMD-0801 will be considered “prior” medications and supplements.

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

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 contract research organization's (CRO's) SOPs.

## 9.2 Electronic Data Capture

Data from the source documents will be entered into the electronic 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 World Health Organization (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 Consolidated Medical Bio-Analysis, Inc. at 10700 Walker Street, Cypress, CA 90630. All lab results will be sent electronically to Integrium. The clinical laboratory results will be imported into the database.

## 9.3 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.

## 11.2 Protection of Human Subjects

### 11.2.1 Declaration of Helsinki

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

### 11.2.2 Good Clinical Practice and Regulatory Compliance

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

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

### 11.2.3 Institutional Review Board

The Investigator is responsible for the submission of the protocol, ICF, and other written materials (such as advertisements and diaries), along with relevant supporting data (e.g., IB), to the appropriate IRB for review and approval before the study can be initiated. The Investigator is also responsible for submitting amendments to the protocol and ICF to the IRB for review and approval prior to implementation of the change. The Investigator is responsible for providing the Sponsor with a letter documenting the IRB approval prior to initiation of the study or implementation of the changes, respectively.

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

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

- IRB for review and approval/favorable opinion.

- The Sponsor via appropriate designees.
- Regulatory Authorities, if required by local regulations.

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

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

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

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

### 11.2.4 Subject Informed Consent

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

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

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

The ICF and any other information provided to subjects will be revised whenever important new information becomes available that is relevant to the subject's consent, and the Investigator will

obtain the IRB's written approval/favorable opinion prior to the use of the revised documents. The Investigator, or a person designated by the Investigator, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. Subjects will read and sign any and all revised ICFs.

## 11.3 Subject Confidentiality

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

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

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

## 11.4 Entering Data Into EDC

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.

## 11.5 Source Documentation

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

## 11.6 Retention of Records

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

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

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

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

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

## 11.7 Clinical Study Report

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

# 12 STUDY ADMINISTRATION

## 12.1 Study Monitoring

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

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

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

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

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

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

## 12.2 On-Site Audits

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

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

## 12.3 Data Quality Assurance

All eCRFs must be completed by authorized Investigational Site personnel who have undergone 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 CRF are accurate and correct by electronically signing and dating the eCRF.

All CRF 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, CRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor and Integrium to the Investigator may not be disclosed to others without direct written authorization from the Sponsor and Integrium, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

# 13 REFERENCES

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