INTEGRIUM, LLC
BIOSTATISTICS AND STATISTICAL PROGRAMMING DEPARTMENT

Clinical Study Protocol: ORA-D-012

A Phase 2a, Randomized, Double-Blind, Double-Dummy, Placebo-Controlled, 3-Way Crossover Study to Compare Safety, Efficacy and Pharmacodynamics of Single and Multiple Doses of ORMD-0801 or Placebo in Adult Subjects with Type 2 Diabetes Mellitus

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Signature Page

Statistical Analysis Plan for Clinical Study Protocol: ORA-D-012

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0.1	O. Lopez	21DEC2016	Initial draft
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Glossary of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Time-Concentration Curve
bid	Twice Daily
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CRU	Clinical Research unit
CSR	Clinical Study Report
CTCAE	Common Terminology for Adverse Events
CV	Coefficient of Variation
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	Hour
ICH	International Conference on Harmonization
IP	Investigational Product
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
N	Sample Size
NCI	National Cancer Institute
PD	Pharmacodynamic
PK	Pharmacokinetic
qd	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T2DM	Type 2 Diabetes Mellitus
TEAE	Tretment-Emergent Adverse Events
tid	Three Times Daily
WHO	World Health Organization

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1. Introduction

1.1. Scope

This document contains detailed information to aid the production of the Clinical Study Report (CSR) including summary tables and listings for trial ORA-D-012**.** The contents of this document were reviewed by the sponsor, Oramed, Ltd., and the trial biostatistician at Integrium.

1.2. Study Overview

This a phase 2a, randomized, double-blind, double-dummy, placebo-controlled, 3-way crossover study enrolling approximately 30 adult subjects with T2DM from age 20 to 75 inclusive. Following a 7-10 day Screening period, eligible subjects will be housed in the CRU for the duration of each treatment cycle beginning with a 3-day single-blind placebo run-in. On Day 4, each subject will be randomized to a treatment sequence that will include three treatment assignments for each of three treatment periods according to the randomization scheme.

All eligible subjects will receive placebo plus two of the following: ORMD-0801 460 IU qd, OMRD-0801 bid, or ORMD-0801 tid. Subjects will receive the randomized treatment from Day 4 through Day 8. A 24-hour single-blind placebo washout will be done on Day 9. Subjects will be discharged on the morning of day 10. Each treatment Period will be separated by a 2-week washout. A final follow-up visit will be performed 1 week after the end of the third treatment period.

In addition, adverse events, clinical laboratory values, vital signs, and electrocardiograms (ECGs) will be evaluated periodically for safety.

1.3. Study Objectives

1.3.1 Primary Objectives

The primary objectives of this study are to compare pre-treatment (Day 3) to end of treatment (Day 8) 24-hour CGM glucose for single and multiple doses of ORMD-0801 vs placebo and to evaluate safety parameters for single and multiple dose of ORMD-0801 vs placebo.

1.3.2 Secondary Objectives

Secondary objectives are:

- To compare pre-treatment (Day 3) to end of treatment (Day 8) mean daytime CGM glucose for single and multiple doses of ORMD-0801 vs placebo.
- To compare pre-treatment (Day 3) to end of treatment (Day 8) mean nighttime CGM glucose for single and multiple doses of ORMD-0801 vs placebo.
- To compare pre-treatment (Day 3) to post-treatment washout (Day 9) 24-hour CGM glucose for single and multiple doses of ORMD-0801 vs placebo.
- To compare post-prandial glucose measurements for single and multiple doses of ORMD-0801 vs placebo.

- To compare pre-treatment (Day 3) to end of treatment (Day 8) insulin pharmacokinetics (PK) for single and multiple doses of ORMD-0801 vs placebo.
- To compare pre-treatment (Day 3) to end of treatment (Day 8) C-peptide pharmacodynamics (PD) for single and multiple doses of ORMD-0801 vs placebo.
- To compare defined events of hypoglycemia for single and multiple doses of ORMD-0801 vs placebo.

1.3.3 Exploratory Objectives

There are no exploratory objectives.

2. Detailed Statistical Methods

2.1. General Statistical Methods

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated by descriptive statistics. For descriptive statistics summary tables will include by study group summaries of sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), median (and other percentiles, if appropriate), minimum and maximum values, and 95% Confidence Intervals (if appropriate). For categorical variables summary tables will include by study group summaries of frequency counts

2.2. Study Populations

Safety population: All patients who receive at least one dose of the study drug will be included in the safety population

Efficacy population: Intent-to-treat (ITT) population with last observation carried forward (LOCF) in patients who receive at least one treatment with study drug and in whom CGM data was collected at least once during treatment.

2.3. Patient Disposition and Characteristics

An account of the patients by disposition will be tabulated overall. The number of patients included in each analysis population will be summarized. Patients not completing the study will be summarized and listed with the reason for their premature discontinuation. There will be an analysis of withdrawal rates by treatment group using both descriptive statistics and Fisher's exact test (2-sided and alpha=0.05). A list of screening failures will also be provided.

2.4. Demographics and Patient Baseline Characteristics

Patient demography will be presented using summary statistics (N, mean, standard deviation, median, minimum and maximum) for continuous measurements, or frequency tables (numbers and percentages) for categorical measurements.

2.5. Study Drug Duration and Compliance

During the run-in period four doses of placebo (8 capsules) will be dispensed to subjects for Day 1 and Day 2. Compliance will be reviewed during admission on Day 2 to protect the single-blind nature of this treatment.

All doses of study treatment will be administered in the CRU. Oral dosing compliance will be ascertained by inspection of the oral cavity (mouth check) following dosing.

This study does not include dose modifications.

2.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug dictionary March 1, 2013 version.

Prior medications will be defined as any medication that stops prior to the day of first dose.

Concomitant medications will be defined as any medication that stops on or after the day of first dose.

Section 2.13 describes the imputation rules for partial dates. All medications will be presented in a data listing.

2.7. Safety Evaluations

2.7.1. Adverse Events

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA) version 16.0 and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. The severity of AEs will be graded according to NCI CTCAE version 4.03.

Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first randomized dose of study treatment on visit 2/Day 4. The incidence of TEAEs will be tabulated by MedDRA preferred term, system organ class, treatment group, severity, and assigned relationship to study treatment. Adverse events will also be summarized by severity and relationship to the investigational product (IP).

The incidence of serious AEs, drug-related AEs, serious and drug-related AEs, and any AEs resulting in discontinuation from the study will be listed.

2.7.2. Hypoglycemic Events

The proportion (percentage) of patients affected by hypoglycemia and event rates for each of the classifications of hypoglycemic events will be reported by treatment received. The time-distribution of hypoglycemic episodes per patient will be reported for each treatment group.

2.7.3. Safety Laboratory Evaluations

Screening and end of study results, together with changes from screening at end of study, will be described using summary statistics for each parameter. Changes from screening will be compared between treatments using an Analysis of Variance (ANOVA) model.

A clinically significant abnormal value or clinically significant change from baseline (Screening), may be recorded as an AE, if deemed appropriate by the PI or sponsor.

2.7.4. Vital Signs

Results, together with changes from baseline, will be described using summary statistics for each parameter for each day in which vital signs are collected. Changes from baseline will be compared between treatments using an ANOVA model.

A clinically significant change from baseline may be recorded as an AE, if deemed appropriate by the PI or sponsor.

2.7.5. Electrocardiogram

Individual 12-lead ECG assessments will be listed by visit.

2.7.6. Physical Examination

The Screening and end of treatment results will be described using frequency counts for each body system.

2.7.7. Continuous Glucose Monitoring

The number of subjects who had at least one value < 60, had at least one value ≥ 125, had at least one value ≥ 150, had at least one value ≥ 175, had at least one value ≥ 200, had at least one value ≥ 225 and had at least one value ≥ 250 will be summarized for the run-in and end of treatment periods for the following time intervals:

- 24 hour
- Daytime
- Nighttime

2.8. Efficacy Evaluations

2.8.1. Continuous Glucose Monitoring

The last 2 days with at least 80% of expected measurements prior to dosing will be considered the run-in days for each of the parameters. The last 2 days with at least 80% of expected measurements prior to 8 hours after the last dose will be considered the on treatment days. The measurements more than 8 hours after the last dose will be considered the follow-up days.

The 24-hr period (6AM to 6AM), nighttime (from 10pm to 6am), daytime (6AM to 10PM), and post-prandial (first hour after meal start time including breakfast, lunch, and dinner) glucose values will be summarized. The mean, standard deviation, minimum, maximum, first quartile, median, third quartile and inner-quartile range will be presented.

The area under the curve (AUC) will be derived for each of the time periods (24-hour, daytime and nighttime) using the indicated days (run-in days, treatment days and follow-up days). The average glucose measurement will be derived by dividing the AUC by the number of observed hours. The average change from run-in will be derived for each treatment regimen for both the treatment days and the follow-up days.

The placebo adjusted change in means will be derived for each of the active therapy regimens by subtracting the placebo mean (the mean change from run-in while the subject was receiving placebo) from the active therapy mean (the mean change from run-in while the subject was receiving the active therapy).

The placebo adjusted change in means will be derived for both the treatment days and the follow-up days. The placebo adjusted change in means will be analyzed using an Analysis of Variance (ANOVA) with treatment as the main effect to determine whether multiple doses a day has an effect on the CGM parameters. If the residuals are not normally distributed, then a Kruskal-Wallis test (one-way analysis of variance on the ranks) will be performed.

The ratios of the placebo adjusted change in means between the active treatments within each subject will also be derived to estimate the magnitude of the dose response.

Summary statistics will be presented for both the placebo adjusted change in means and the ratios of the placebo adjusted change in means. Analysis results will be presented for the change in means.

2.8.2. Pharmacokinetic / Pharmacodynamic Evaluations

Since Insulin is present in the subjects regardless of treatment, standard PK derivations do not apply.

The PK/PD measurements are taken pre-treatment (Day 3) and at end of treatment (Day 8). On Day 3, all subjects received Placebo, so these measurements will be used as the within subject control.

Time matched changes between Day 8 and Day 3 will be derived for the PK and PD parameters for each subject.

The following time intervals will be summarized: 0 to 60 minutes, 60 to 120 minutes, 120 to 180 minutes, 180 to 240 minutes, 240 to 300 minutes, 120 to 300 minutes and 180 to 300 minutes. Please note that the 0 to 60 minute interval will not be summarized, since it is believed that the study drug takes 60 minutes to metabolize.

The following parameters will be derived for Insulin C-Peptide for each subject:

- Positive Area (Area above 0),
- Negative Area (Area below 0),
- Absolute Area (Positive Area + the absolute value of the Negative Area),
- Maximum Difference,
- Time of Maximum Difference,
- Positive Area / hr (for the 120 to 300 minutes and 180 to 300 minutes intervals only),
- Negative Area / hr (for the 120 to 300 minutes and 180 to 300 minutes intervals only), and
- Absolute Area / hr (for the 120 to 300 minutes and 180 to 300 minutes intervals only).

The Positive Areas, Negative Areas and Absolute Areas will be compared using a one-way analysis of variance (ANOVA) with Fisher's LSD being used for pairwise treatment group comparisons.

The maximum difference and time of maximum difference will be compared in a pairwise fashion using the Wilcoxon Rank Sum test.

The PK/PD analysis will be conducted using model-independent methods and will be based on plasma concentrations of insulin and C-peptide. Individual plasma concentrations of insulin and C-peptide will be listed for each subject and sampling time and summarized descriptively using the arithmetic mean, SD, CV (%), median, minimum and maximum. Individual plasma concentration-time profiles of insulin and C-peptide will be plotted on both a linear and a semi-logarithmic scale. Mean values will also be presented graphically.

2.9. Interim Analyses

No interim analyses are planned.

2.10. Other Analyses

No other analyses are planned at this time.

2.11. Sample Size and Power Considerations

A total of 30 subjects will be randomized to receive either placebo, ORMD-0801 460 IU qd, ORMD-0801 460 IU bid, or ORMD-0801 460 IU tid during each treatment period.

This study is not powered for statistical significance.

2.12. Randomization Scheme and Codes

The randomization details are documented in a separate randomization plan.

2.13. Handling Missing Data

Listings will be provided for all data. Descriptive statistics will be provided for all planned visits as provided on the Case Report Forms (CRFs).

Study days will be analyzed using the study days as reported in the Case Report Form. Likewise, unscheduled visits will not be reassigned a visit number based on the visit date.

Dates related to the adverse events and medications will be imputed using the rules below in an effort to categorize them properly into the summary tables.

Imputing partial or missing start dates:

- If the year is unknown, then the start date will not be imputed. The date will remain missing.
- If the month is unknown and the year is the same as the first dose date of the study, then impute the month and day of the date to be equal to the first dose month and day. Otherwise, impute the month as January.
- If the day is unknown and the month and year are the same as the first dose date of the study, then impute the day to be equal to the day of the first dose. Otherwise, impute the day as '01'.

Impute partial or missing stop dates:

- If the year is unknown, then the stop date will not be imputed. The date will remain missing.
- If the month is unknown, impute the month as December.
- If the day is unknown, impute the day to be the last day of the month.

If an imputed stop date is greater than the date of study completion/discontinuation date of the study, then the imputed stop date will be set equal to the date of completion/discontinuation date.

The imputed dates will be stored in the analysis datasets along with the original dates as recorded by the sites.

Efficacy analyses will be performed for the ITT population in which CGM data was collected during treatment. The weighted mean night time glucose levels will be calculated on CGM data as described in Section 2.8.1. No imputation will be used other than application of linear interpolation for calculation of the trapezoidal areas.

2.14. Protocol Deviations

Protocol deviations will be displayed in a data listing as provided by the clinical team.

2.15. Computer Systems and Packages Used for Statistical Analyses

SAS® version 9.4 on the Microsoft Windows 7 64 bit platform will be used for all analyses. All computations will be performed using SAS®. The exact form of the various algorithms will be the SAS® defaults. The output from any SAS® procedure will be used in the tables using SAS® macros.

3. Data Listing Shells

3.1. Data Listings Table of Contents

The following post-text listings will be generated.

16.1.7	Randomization Schedule
16.2.1	Subject Completion/Discontinuation
16.2.2	Protocol Deviations
16.2.3	Population Status
16.2.4.1	Demographics and Baseline Characteristics
16.2.4.2.1	Substance Use – Alcohol Potential
16.2.4.2.2	Substance Use – Tobacco / Nicotine Potential
16.2.4.2.3	Substance Use – Caffeine Potential
16.2.4.3	Subject Eligibility and Informed Consent
16.2.4.4	Medical History / Surgical History / Procedures
16.2.4.5	Prior and Concomitant Medications
16.2.5	Drug Accountability
16.2.6.1	Continuous Glucose Monitoring – 24-hour Mean Values
16.2.6.2	Continuous Glucose Monitoring – Daytime Mean Values
16.2.6.3	Continuous Glucose Monitoring – Nighttime Mean Values
16.2.6.4	Fasting Blood Glucose
16.2.6.5	Post-Prandial Blood Glucose – Breakfast, Lunch, and Dinner
16.2.6.6.1	Serum Insulin Levels
16.2.6.6.2	Serum Insulin Parameters
16.2.6.7.1	C-peptide Levels
16.2.6.7.2	C-peptide Parameters
16.2.7.1	Adverse Events

16.2.7.2	Hypoglycemic Events
16.2.8	Safety Laboratory Test Results
16.2.9.1	Vital Signs
16.2.9.2	Electrocardiogram Results
16.2.9.3	Physical Examination Results
16.2.9.4	Continuous Glucose Monitoring – Values Outside Observed Value Reference Ranges

3.2. Data Listings

All subjects and all data will be presented in the listings. The listings will be sorted by treatment and subject number.

4. Summary Table and Figure Shells

4.1. Post-text Table of Contents

The following post-text tables will be generated.

Table Number	Table title
14.1.1.1	Summary of Subject Screening Disposition (All Subjects)
14.1.1.2	Summary of Subject Disposition (Safety Population)
14.1.1.3	Summary of Subject Disposition (ITT Population)
14.1.2.1	Summary of Demographics and Baseline Characteristics (Safety Population)
14.1.2.2	Summary of Demographics and Baseline Characteristics (ITT Population)
14.1.3	Summary of Medical History / Surgical History / Procedures (Safety Population)
14.1.4.1	Summary of Prior Medications (Safety Population)
14.1.4.2	Summary of Concomitant Medications (Safety Population)
14.1.5.	Summary of Study Medication Usage (Safety Population)
14.2.1.1	Summary of Pre-treatment (day 3) to end of Treatment (day 8) Continuous Glucose Monitoring Mean 24-hour Glucose – (ITT Population)
14.2.2.1	Summary of Pre-treatment (day 3) to end of Treatment (day 8) Continuous Glucose Monitoring Mean Daytime Glucose – (ITT Population)
14.2.2.2	Summary of Pre-treatment (day 3) to end of Treatment (day 8) Continuous Glucose Monitoring Mean Nighttime Glucose – (ITT Population)

Table Number	Table title
14.2.3.1	Summary of Pre-treatment (day 3) to Post Treatment Washout (day 9) Continuous Glucose Monitoring Mean 24-hour Glucose – (ITT Population)
14.2.4.1	Summary of Post-Prandial (Breakfast, Lunch, and Dinner) Glucose Measurements – (ITT Population)
14.2.5.1	Insulin Levels by Time Point (ITT Population)
14.2.5.2	Insulin Parameters by Time Intervals (ITT Population)
14.2.6.1	C-Peptide Levels by Time Point (ITT Population)
14.2.6.2	C-Peptide Parameters by Time Intervals (ITT Population)
14.3.1.1	Adverse Events Overall Summary (Safety Population)
14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class, and Preferred Term (Safety Population)
14.3.1.3	Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study (Safety Population)
14.3.1.4	Summary of Serious Treatment Emergent Adverse Events (Safety Population)
14.3.1.5	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity (Safety Population)
14.3.2	Summary of Laboratory Values (Safety Population)
14.3.3	Summary of Vital Signs (Safety Population)
14.3.4	Summary of Hypoglycemic Events (Safety Population)
14.3.5	Summary of Physical Examination Findings (Safety Population)
14.3.6.1	Continuous Glucose Monitoring – Number of Subjects Outside Observed Value Reference Ranges by Day (Safety Population)
14.3.6.2	Continuous Glucose Monitoring – Number of Subjects Outside Observed Value Reference Ranges by Number of Days (Safety Population)

4.2. Post-text Figures Tables of Contents

The following post-text figures will be generated.

Figure Number	Figure Title
14.2.1.1	Mean Daytime Continuous Glucose Monitoring Values by Day (ITT Population)
14.2.1.2	Mean Nighttime Continuous Glucose Monitoring Values by Day (ITT Population)
14.2.1.3	Individual Continuous Glucose Monitoring Values Over Time (ITT Population)
14.2.1.4	Individual Continuous Glucose Monitoring Values by Subject (ITT Population)
14.2.2.1	Mean Insulin Levels by Time (ITT Population)
14.2.2.2	Individual Insulin Levels Over Time (ITT Population)
14.2.2.3	Individual Insulin Levels by Subject (ITT Population)
14.2.3.1	Mean C-Peptide Levels by Time (ITT Population)
14.2.3.2	Individual C-Peptide Levels Over Time (ITT Population)
14.2.3.3	Individual C-Peptide Levels by Subject (ITT Population)
14.2.4	Integrated Insulin and C-Peptide Levels by Subject (ITT Population)

4.3. Table Shells

The table shells can be found in a separate file. The following number of decimal places will be used when presenting summary statistics:

- N to 0 decimal places
- Minimum and maximum to the same number of decimal places as recorded in the raw data.
- Means and medians to 1 more decimal place than is recorded in the raw data. Standard deviations to 2 more decimal places than is recorded in the raw data.
- Percentages to 1 decimal place.

The precision may be changed for individual endpoints as needed.