INTEGRIUM, LLC
BIOMETRICS DEPARTMENT

Clinical Study Protocol: ORA-D-017

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

Statistical Analysis Plan (SAP) Documentation

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Glossary of Abbreviations

AE	Adverse Event
AUC	Area Under the Time-Concentration Curve
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
IP	Investigational Product
HbA1c	Hemoglobin A1c
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
PI	Primary Investigator
QD	Once a Day
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
T1D	Type 1 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Events
TID	Three Times a Day
WHO	World Health Organization

Table of Contents

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-017**.** The contents of this document were reviewed by the sponsor, Oramed Pharmaceuticals, Inc., and the trial biostatistician at Integrium.

1.2. Study Overview

This study is designed to compare ORMD-0801 given once a day (QD) versus three times a day (TID) in subjects with Type 1 Diabetes (T1D). The study will consist of seven visits (including Screening Visit).

Subjects will come in for a screening visit to determine eligibility for participation in the study. Eligible subjects will be scheduled to return to the clinic approximately 1 week later. Subjects fulfilling all inclusion/exclusion criteria will have a Continuous Glucose Monitor (CGM) placed, provided with a diary, dispensed placebo capsules and asked to return to the clinic in approximately 10 days for randomization.

At the randomization visit (Visit 3), data from the CGM will be downloaded and diaries will be collected and reviewed. 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 return to the clinic in eighteen days for the next visit (Day 18). On Day 18 (Visit 4), a CGM will be placed and a diary will be provided.

Subjects will return to the clinic ten days following Visit 4, on Day 28 (Visit 5). Compliance will be assessed, data from the CGM will be downloaded, the diary will be collected, and subjects will be crossed over to the alternate treatment regimen.

Subjects will be instructed to return to the clinic in 18 days for the next visit (Day 46). On Day 46 (Visit 6), a CGM will be placed and a diary will be provided.

Subjects will return to the clinic on Day 56 (Visit 7) compliance will be assessed, data from the CGM will be downloaded and diary will be collected.

1.3. Study Objectives

1.3.1 Primary Objectives

The primary objectives of the study are:

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 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 CGM over the last 10 days of each treatment period.

1.3.2 Secondary Objectives

The secondary objectives of this study are:

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 glucodynamic 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 tests results (hematology, chemistry and urinalysis) and vital signs.

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

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.

2.4. Demographics and Patient Baseline Characteristics

Demographic and baseline characteristics will be summarized for all subjects. Summary statistics (e.g., number of subjects, mean, median, standard deviation, minimum and maximum) will be generated for continuous variables (e.g., age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (e.g., sex, ethnicity and race).

2.5. Study Drug Duration and Compliance

This is a two-period crossover study. A table summarizing the number of days on study medication, the number of tablets taken and the percent compliance (100*number of tablets taken / expected number of tablets) by treatment regimen will be presented.

2.6. Prior and Concomitant Medications

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug dictionary March 2018 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 21.0 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.

Treatment-emergent adverse events (TEAEs) are defined as any AE that starts or increases in severity after the first randomized dose of study treatment. 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 will be reported by treatment regimen. The hypoglycemic information will come from the data entered in the Hypoglycemic / Hyperglycemic log.

2.7.3. Safety Laboratory Evaluations

Screening, pre-dose values (Day 1 of treatment), post-dose values (Day 28 of treatment) and change from pre-dose to post-dose will be described using summary statistics for each parameter for each treatment regimen. All laboratory results will be presented in listings.

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

Screening, pre-dose values (Day 1 of treatment), Day 18 of treatment, Day 28 of treatment and change from pre-dose to Days 18 and 28 will be described using summary statistics for each parameter for each treatment regimen. All vital sign results will be presented in listings.

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

2.7.5. Electrocardiogram

ECG was collected at screening only. All ECG results will be presented in listings.

2.7.6. Physical Examination

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

All physical exam findings will be presented in the data listings.

2.8. Efficacy Evaluations

The primary endpoints for the study are:

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.

The secondary endpoints for the study are:

1. 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})
2. Total daily non-oral insulin requirements in units per kilogram (kg) body weight over the last 10 days of each treatment period.

The exploratory endpoints for the study are:

1. HbA1c measured at the end of each treatment period
2. Patient diary-reported carbohydrate intake over the final 10 days of each treatment period
3. Changes in body weight from baseline (Visit 3) to the end of each treatment period
4. Other measures of hypoglycemia
    a. Severe hypoglycemia 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)
    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.

2.8.1. 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 measurement. When analyzing the exogenous insulin variables, the CGM parameters (mean 24 hour glucose value and 24 hour time within 70-180 mg/dL range) and the patient reported carbohydrate intake will be included as covariates. When analyzing CGM parameters, the 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 (Day 28 and Day 56) 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.

2.8.2. Basal, Bolus and Total Exogenous Insulin

The amount of basal, bolus and total exogenous insulin will be analyzed using the Repeated Masures Analysis of Covariance model indicated in Section 2.8.1. Least squares mean, 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.

2.8.3. Continuous Glucose Monitoring

Continuous Glucose Monitoring (CGM) will be summarized using 3 different time intervals:

- Daytime (6AM to 10PM),
- Nighttime (10PM to 6AM) and
- 24 Hour (6AM to 6AM).

The area under the curve (AUC) will be derived for each of the time periods 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 for each time interval:

- Time that Glucose Value is Between 70 and 180,
- Time that Glucose Value is Less Than 70,
- Time that Glucose Value is Greater Than 180,

- Time that Glucose Value is Greater Than 250,
- Low Blood Glucose Index, and
- 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 2.8.1.

Individual and mean figures will be generated to present the glucose curves / data for the 24-hour, daytime and nighttime measurements.

2.8.4. 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 2.8.1.

2.9. Interim Analyses

There are no interim analyses planned for this study.

2.10. Other Analyses

No other analyses are planned at this time.

2.11. Sample Size and Power Considerations

An estimated total of approximately 26 subjects are planned to be randomized to participate in the two dosing conditions in a randomized order. The study objectives (primary and secondary) have not been previously explored, so there are no estimates of means or standard deviations to perform power calculations.

2.12. Randomization Scheme and Codes

The randomization details for this study are presented 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 electornic Case Report Forms (eCRFs).

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.

There is no plan to impute missing CGM data.

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

Server SAS® version 9.4 on the Microsoft Windows Server 2008R2 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	Childbearing Status
16.2.4.3	Inclusion / Exclusion Criteria and Informed Consent
16.2.4.4	Medical History
16.2.4.5.1	Prior and Concomitant Medications
16.2.4.5.2	Non-Drug Treatment
16.2.5.1	Study Drug Accountability
16.2.5.2	Study Drug Dosing Time – Final 10 Days of Treatment
16.2.6.1	Exogenous Insulin Usage – Final 10 Days of Treatment
16.2.6.2.1	Continuous Glucose Monitoring – Daytime Parameters
16.2.6.2.2	Continuous Glucose Monitoring – Nighttime Parameters
16.2.6.2.3	Continuous Glucose Monitoring – 24 Hour Parameters
16.2.6.4	Carbohydrate Intake – Final 10 Days of Treatment
16.2.6.5	HbA1c Values
16.2.6.6	Weight Values
16.2.7.1.1	Adverse Events
16.2.7.1.2	Serious Adverse Events
16.2.7.1.3	Adverse Events Leading to Study Treatment Discontinuation
16.2.7.2	Hypoglycemic / Hyperglycemic Log
16.2.8.1	Laboratory Test Results - Chemistry
16.2.8.2	Laboratory Test Results - Hematology
16.2.8.3	Laboratory Test Results – Urinalysis
16.2.9.1	Vital Signs
16.2.9.2	Electrocardiogram Results

16.2.9.3	Physical Examination Results

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.

There are currently 29 listings that are planned to be generated. The 29 listings are broken down as follows: 16 Standard Unique, 4 Standard Repeat, 9 Non-Standard Unique and 0 Non-Standard Repeat.

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	Summary of Subject Disposition (Safety Population)
14.1.2	Summary of Demographics and Baseline Characteristics (Safety Population)
14.1.3	Summary of Medical History (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 Compliance (Safety Population)
14.2.1	Summary of Exogenous Insulin Usage (Safety Population)
14.2.2.1	Summary of Continuous Glucose Measurement Parameters – Daytime (Safety Population)
14.2.2.2	Summary of Continuous Glucose Measurement Parameters – Nighttime (Safety Population)
14.2.2.3	Summary of Continuous Glucose Measurement Parameters – 24-Hour (Safety Population)
14.2.3	Summary of Carbohydrate Intake (Safety Population)
14.2.4	Summary of HbA1c (Safety Population)
14.2.5	Summary of Weight (Safety Population)
14.3.1.1	Adverse Events Overall Summary (Safety Population)

Table Number	Table title
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)
14.3.1.6	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Treatment (Safety Population)
14.3.2.1	Summary of Laboratory Values – Chemistry (Safety Population)
14.3.2.2	Summary of Laboratory Values – Hematology (Safety Population)
14.3.2.3	Summary of Laboratory Values – Urinalysis (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)

4.2. Summary Tables

There are currently 25 tables that are planned to be generated. The 25 tables are broken down as follows: 9 Standard Unique, 4 Standard Repeat, 12 Non-Standard Unique and 0 Non-Standard Repeat.

4.3. Post-text Figures Tables of Contents

The following post-text figures will be generated.

Figure Number	Figure Title
14.2.1.1.1	Exogenous Insulin Usage - Basal – Individual Observed Values
14.2.1.1.2	Exogenous Insulin Usage - Basal – Mean Observed Values
14.2.1.2.1	Exogenous Insulin Usage - Bolus – Individual Observed Values
14.2.1.2.2	Exogenous Insulin Usage - Bolus – Mean Observed Values
14.2.1.3.1	Exogenous Insulin Usage - Total – Individual Observed Values
14.2.1.3.2	Exogenous Insulin Usage - Total – Mean Observed Values
14.2.2.1.1	Continuous Glucose Measurements - Individual Observed Values – 24-Hours
14.2.2.1.2	Continuous Glucose Measurements - Mean Observed Values – 24-Hours

Figure Number	Figure Title
14.2.2.2.1	Continuous Glucose Measurements - Individual Observed Values – Daytime
14.2.2.2.2	Continuous Glucose Measurements - Mean Observed Values – Daytime
14.2.2.3.1	Continuous Glucose Measurements - Individual Observed Values – Nighttime
14.2.2.3.2	Continuous Glucose Measurements - Mean Observed Values – Nighttime

4.4. Post-Text Figures

There are currently 12 figures that are planned to be generated. The 12 figures are broken down as follows: 0 Standard Unique, 0 Standard Repeat, 8 Non-Standard Unique and 4 Non-Standard Repeat.

4.5. 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.