Study Protocol Number: **R477-202**

Statistical Analysis Plan Date: **12 July 2019**

Official Title: **A Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of Multiple Doses of REMD-477 in Subjects With Type 1 Diabetes Mellitus**

NCT Number: **NCT03117998**

STATISTICAL ANALYSIS PLAN

A Randomized, Placebo-controlled, Double-blind Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of Multiple Doses of REMD-477 in Subjects with Type 1 Diabetes Mellitus

Statistical Analysis Plan Status: Final Amendment 1
Statistical Analysis Plan Date: 12 July 2019

Study Drug: REMD-477

Sponsor Reference Number: R477-202
Covance Study Number: 8365602

Clinical Phase 2

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical, safety, efficacy and pharmacodynamic (PD) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

E. L. Warriner — 15 Jul 2019

Emma Warriner, MSc
Statistician

Date

Sponsor approval:

12 July, 2019

Dung "Zung" Thai, MD, PhD
Chief Medical Officer
REMD Biotherapeutics, Inc.

Date

15 July 2019

Edgar Bautista
Clinical Operations Director
REMD Biotherapeutics, Inc.

Date

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3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
ACT	arginine challenge test
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	area under the concentration-time curve
CDISC	Clinical Data Interchange Standards Consortium
CGM	continuous glucose monitoring
CI	confidence interval
CSR	Clinical Study Report
CV	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
eCRFs	electronic Case Report Forms
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
ICH	International Conference on Harmonisation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed Meal Tolerance Test
ms	millisecond
OBV	overnight baseline visit
PD	pharmacodynamics
PK	pharmacokinetic
QOL	Quality of Life
QTc	QT correction; QT interval corrected for heart rate
QTcB	QTc calculated using the Bazett correction
QTcF	QTc calculated using the Fridericia correction
SAP	Statistical Analysis Plan

SC	subcutaneous
T1-DDS	Type 1 – Diabetes Distress Scale
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 03 April 2017 and Protocol Amendment 2 dated 26 October 2019).

This SAP describes the planned analysis of the efficacy, PD, safety, and tolerability data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of safety, tolerability, efficacy, PK and PD data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between REMD Biotherapeutics and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between REMD Biotherapeutics and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

5.1 Primary Objective

- To compare the effects of multiple doses of REMD-477 versus placebo on change from baseline at Week 12 in daily insulin requirements.

5.2 Secondary Objectives

- To compare the effects of multiple doses of REMD-477 versus placebo on measures of glycemic control including change from baseline at Week 13 in fasting glucose and glucose area under the curve (AUC) after mixed meal tolerance test (MMTT) – Part A only.

- To compare the effects of multiple doses of REMD-477 versus placebo on change from baseline at Week 12 in average daily 24-h blood glucose concentration and time within target range as assessed by continuous glucose monitoring (CGM) and seven-point glucose profile.

- To compare the effects of multiple doses of REMD-477 versus placebo on the product of the ratio of average glucose (Week 12/Baseline) and ratio of average insulin use (Week 12/Baseline).

- To evaluate the safety and tolerability of multiple doses of REMD-477 versus placebo.

- To compare the incidence of hypoglycemic episodes after multiple doses of REMD-477 versus placebo.

- To compare the effects of multiple doses of REMD-477 versus placebo on change from baseline at Week 13 in hemoglobin A1c (HbA1c).

- To compare the proportion of subjects who achieve HbA1c reduction of ≥ 0.4% after multiple doses of REMD-477 versus placebo at Week 13.

- To compare the effects of multiple doses of REMD-477 versus placebo on pancreatic beta cell function as measured by change from baseline at Week 13 in C-peptide AUC after a MMTT and arginine challenge test (for a subset of subjects who were enrolled prior to Protocol Amendment #1) – Part A only.

- To compare the effects of multiple doses of REMD-477 versus placebo on pancreatic alpha cell function as measured by change from baseline at Week 13 in peripheral levels of fasting glucagon, active and total glucagon-like peptide 1 (GLP-1), and glucagon and GLP-1 (active and total) AUC after MMTT – Part A only.

- To determine REMD-477 plasma concentrations and formation of anti-REMD-477 antibodies after multiple dosing.

5.3 Exploratory Objectives

- To compare the effects of multiple doses of REMD-477 versus placebo on change from baseline at Week 13 in body weight.

- To compare the effects of multiple doses of REMD477 versus placebo on change from baseline at week 13 in Quality of Life (QOL) score.

- To explore the effects of multiple doses of REMD-477 on the intrahepatic lipid content as measured by magnetic resonance imaging – proton density fat fraction (MRI-PDFF) (for a subset of subjects in Part B only)

- To explore the effects of multiple doses of REMD-477 on the intrahepatic lipid content as measured by FibroScan® (for a subset of subjects in Part B only)

6 STUDY DESIGN

This is a randomized, placebo-controlled, double-blind study to evaluate the efficacy, safety, and PD of multiple doses of REMD-477 in subjects who have Type 1 diabetes and are currently receiving insulin treatment. This study will determine whether glucagon receptor blockade with REMD-477 can decrease daily insulin requirements and improve glycemic control after 12 weeks of treatment in subjects diagnosed with Type 1 diabetes with fasting C-peptide < 0.7 ng/mL at Screening.

The two part study (Parts A and B) will be conducted at multiple sites in the United States. In each part, approximately 75 subjects (150 subjects in total across Parts A and B) with Type 1 diabetes on stable doses of insulin will be randomized in a 1:1:1 fashion into one of three treatment groups (placebo, 35 mg REMD-477, or 70 mg REMD-477). The enrollment of Part B may be initiated prior to the completion of Part A. Subjects will receive once weekly SC injections of investigational product for 12 weeks and be followed for an additional 12 weeks during washout in the Safety Follow-up Period. At baseline, throughout the treatment period, and during the 12-week Safety Follow-up Period, subjects will be evaluated for measures of glycemic control, daily insulin requirements, and safety. For subjects enrolled in Parts A and B, CGM and seven-point glucose profile will be conducted to assess the effect of REMD-477 versus placebo on glucose variability and metabolic control. For a subset of subjects in Part A who were enrolled prior to Protocol Amendment #1, beta cell function after mixed meal and ariginine challenge will be examined. For subjects in Part A, alpha cell function will be assessed by measuring fasting glucagon, active and total GLP-1, and glucagon and GLP-1 (active and total) AUC after the MMTT.

For a subset of subjects in Part A who were enrolled prior to Protocol Amendment #1, eligible subjects will be admitted to the clinical research unit (CRU) on the evening of the Overnight Baseline Visit (OBV) (which can occur between Study Day -8 to Day -2), the Week 13 Visit (admission Day 84), and the Week 24 Visit (admission Day 161). For ongoing subjects at the time of the Protocol Amendment #1, the overnight admissions to the CRU at Baseline, Week 13 and Week 24 will not occur.

For a subset of subjects in Part B, the magnetic resonance imaging – proton density fat fraction (MRI-PDFF) and FibroScan® (where feasible) will be performed prior to dosing on Day 1 (or up to 7 days prior to the Day 1 visit, after all other inclusion and exclusion criteria have been met) and on Day 85 (+/- 2 days) of Week 13.

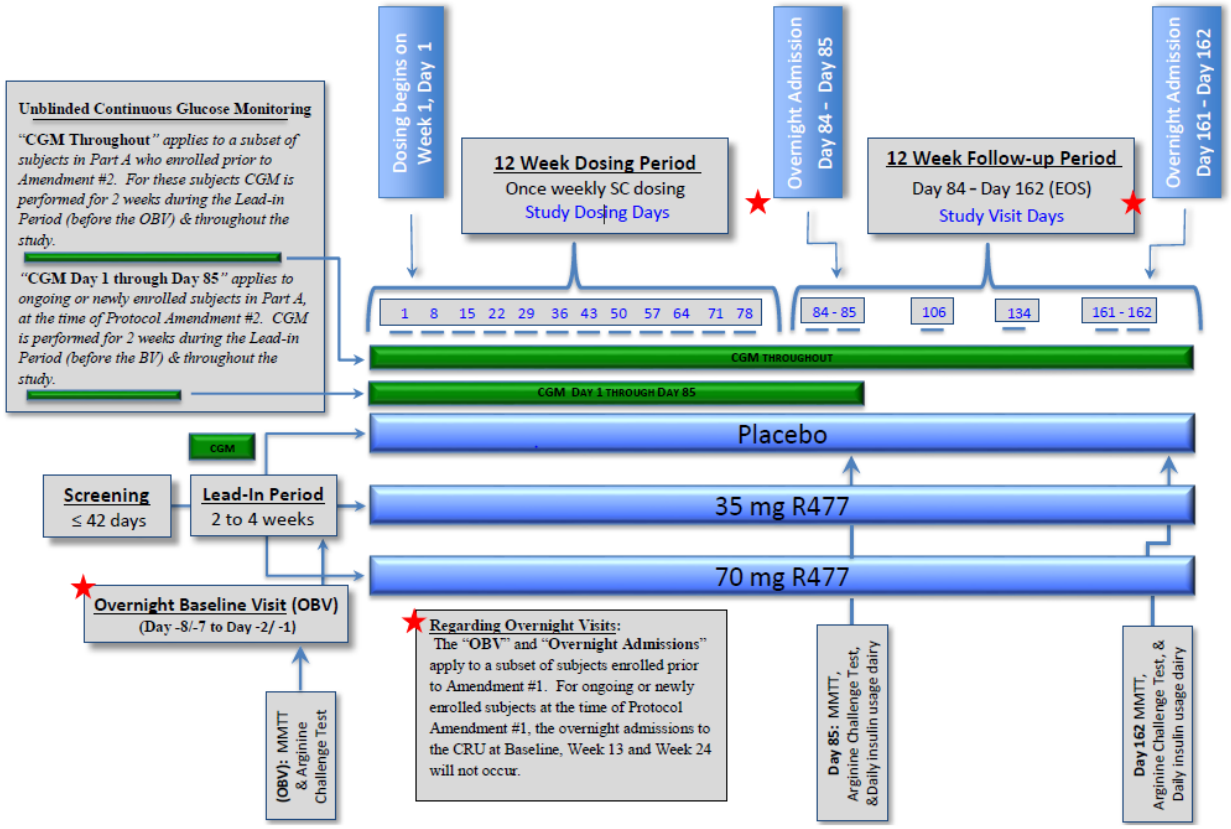

Figure 1: Part A Study Design Schema

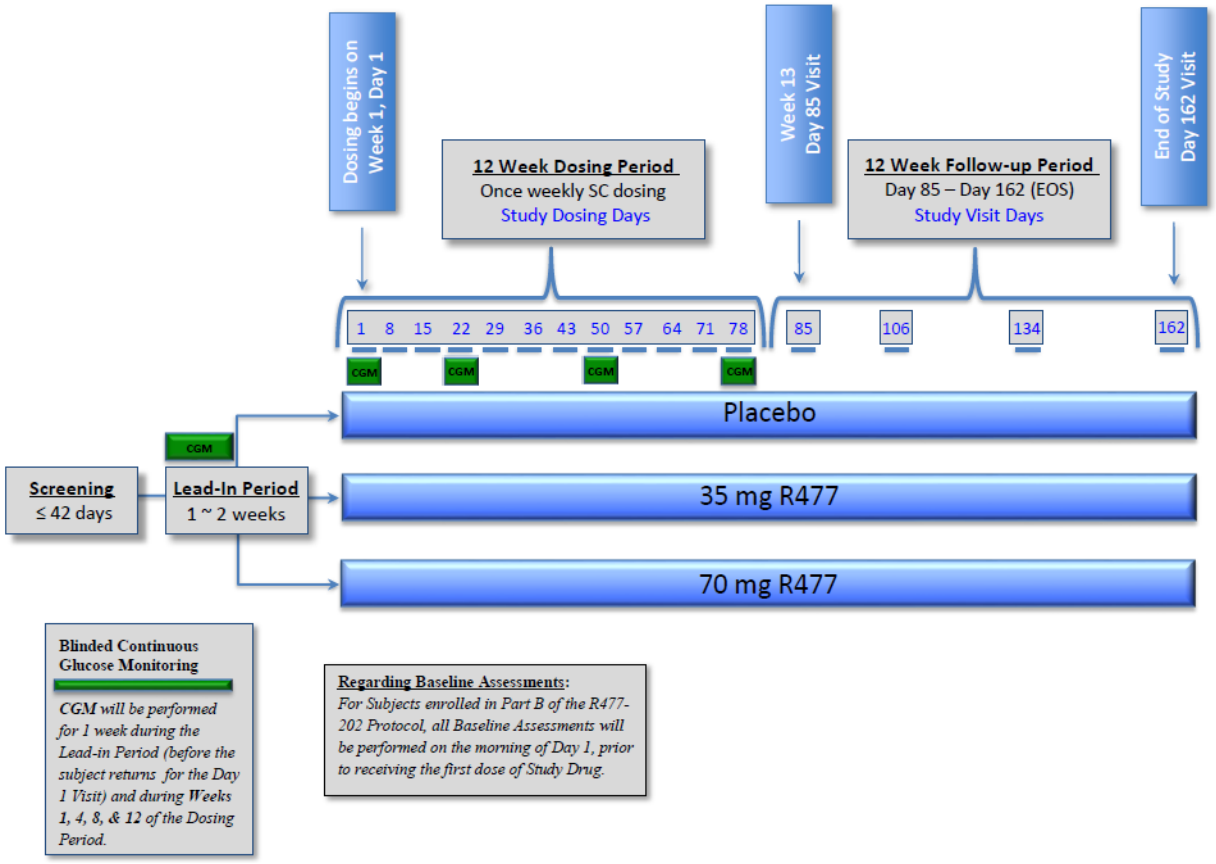

Figure 2: Part B Study Design Schema

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Study Treatment Name	Treatment Order on TFLs
35 mg REMD-477 (SC)	1
70 mg REMD-477 (SC)	2
Placebo (SC)	3

8 SAMPLE SIZE JUSTIFICATION

The power calculation for the primary endpoint (difference in the change from baseline in daily insulin use) is based on the assumption that daily insulin requirement will not change in the

placebo group and will decrease in the REMD-477 treatment groups. Based on an expected coefficient of variation of the daily insulin requirement of ~36%, it is estimated that ≥ 22 subjects in each group (treatment and placebo) will be sufficient to detect a difference of at least 30% with a power of 0.8, and an alpha value of 0.05. To ensure statistical power, and to avoid inadequacy due to unanticipated subject dropout, an N=25/group is used for each Part of this study.

9 DEFINITION OF ANALYSIS POPULATIONS

The analysis populations apply to both Parts A and B separately.

The **All Subjects Population** will consist of any subjects who enrolled on to the study (signed informed consent) and had study assessments recorded on the database as per the protocol.

The **Efficacy Population** will consist of all subjects who received at least one dose of REMD-477 and have evaluable average daily insulin use data.

The **PD Population** will consist of all subjects who received at least one dose of study drug (REMD-477 or placebo) and have evaluable PD data.

The **Safety Population** will consist of all subjects who received at least one dose of study drug (REMD-477 or placebo) and have at least one post-dose safety assessment.

The **PK Population** will consist of all subjects who received at least one dose of REMD-477 and have evaluable PK data.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be summarized and listed.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK/PD).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the Mixed Meal Tolerance Test [MMTT] parameters: areas under the concentration-time curve [AUCs]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Outputs will be created separately for Parts A and B.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and Change from Baseline

Unless otherwise stated, the baseline for each parameter is defined as the last value measured prior to first dosing, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). For ECGs taken in triplicate, baseline will be the mean of the last three values taken prior to first dosing.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Mean percent change from baseline is the mean of all individual subjects' percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the desired timepoint and then dividing this calculated value by the individual subject's baseline value and multiplying by 100. These individual subjects' percent changes from baseline values will be used to calculate the mean percent change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as pre-dose repeats. Post-dose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated, the last three readings are used in all subsequent calculations**.**

All results not taken at a scheduled timepoint for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Subject Disposition, Demographics and Baseline Characteristics

Subject disposition will be summarized and listed for Parts A and B separately.

The demographic variables age, sex, child-bearing potential, race, ethnicity, body weight, height, and body mass index will be summarized and listed for Parts A and B separately.

The duration history of type I diabetes mellitus will be calculated based on the information provided on the medical history electronic case report form (eCRF).

The baseline medical history and concomitant medications will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term and World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) codes for each treatment group, respectively. These data will also be listed for Parts A and B separately.

10.3 Efficacy and Pharmacodynamic Assessments

10.3.1 Efficacy Primary Endpoint

- Change from baseline at Week 12 in daily insulin use.

10.3.2 Secondary Pharmacodynamic Endpoints

- Change from baseline at Week 13 in fasting glucose and glucose AUC after the MMTT – Part A only.
- Change from baseline at Week 12 in average daily 24-h blood glucose concentration and time within target range as assessed by CGM and seven-point glucose profile.
- The product of the ratio of average glucose (Week 12/Baseline) and ratio of average insulin use (Week 12/Baseline).
- Change from baseline at Day 85 (Week 13) in HbA1c.
- Proportion of subjects who achieve HbA1c reduction of $\geq 0.4\%$.
- Change from baseline at Day 85 (Week 13) in fasting C-peptide and C-peptide AUC after MMTT and arginine challenge (for a subset of subjects who were enrolled prior to Protocol Amendment #1) – in Part A only.
- Change from baseline at Day 85 (Week 13) in peripheral levels of fasting glucagon, active and total GLP-1, and glucagon and GLP-1 (active and total) AUC after MMTT challenge – in Part A only.

10.3.3 Exploratory Endpoints

- Change from baseline at Day 85 (Week 13) in body weight.
- Change from baseline in QOL score at Day 84 (Week 13).
- Changes in intrahepatic lipid content as measured by MRI-PDFF (for a subset of subjects in Part B only)
- Changes in intrahepatic lipid content as measured by FibroScan® (for a subset of subjects in Part B only who underwent Fibroscan at baseline and post-treatment)

10.3.4 Efficacy and Pharmacodynamic Statistical Methodology

10.3.4.1 General

All data, including derived parameters, will be listed and summarized for Part A and B separately. Absolute changes (and percentage changes, where applicable) from baseline will also be listed and summarized. Values outside the reference ranges will be flagged, if appropriate.

Preliminary analyses of variance will be performed to assess whether the baseline average daily insulin use and HbA1c levels among subjects are similar between the treatment groups. If any significant difference exists between any two treatments at the 5% level ($p \leq 0.05$), the variable will be used as a covariate in the repeated measures analysis of covariance (ANCOVA) as described in this section to adjust for any pre-intervention difference between treatment groups.

In all analyses, careful attention will be given to the appropriateness of the statistical procedure by determining whether necessary conditions are satisfied; e.g., normality and equal variance. When conditions are violated, the use of data transformations intended to produce data that satisfy normality and equal variance assumptions will be explored. If an appropriate transformation cannot be found, non-parametric methods may be used as an alternative to the more standard analyses.

For all repeated measures ANCOVA of efficacy and pharmacodynamic endpoints, the SAS codes used will be similar to the following:

```
proc mixed data=xxx;
class subject day treatment;
model variable = baseline subject treatment day treatment*day;
repeated day / subject=subject type=csh;
lsmeans treatment*day / pdiff cl alpha=0.05;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

10.3.4.2 Efficacy - Daily Insulin Use

Hypothesis:

Multiple doses of REMD-477 will significantly decrease daily insulin use versus placebo treatment at Week 12.

The daily insulin use will be derived as the average daily insulin over a collection period ranging from either 3 or 7 days. For the Lead-In Period (Part A – 14 to 28 days; Part B – 7 to 14 days), the average daily insulin use will be derived from a period of 14 days. For Days 1, 8, 15, and 22, the average daily insulin use will be derived from the individual insulin values over the next 7 days. For Days 50, 78, 106 and 134, the average daily insulin use will be derived from the individual insulin values over the next 3 days. Baseline assessment is the derived average daily insulin use during the Lead-In (Part A – 14 to 28 days; Part B – 7 to 14 days) period. The measurements will be summarized separately for Parts A and B by treatment group and timepoint along with changes and percentage changes from baseline. Figures of mean average daily insulin use, changes and percentage changes from baseline will be presented separately for Parts A and B by treatment.

The changes from baseline and percentage change from baseline measurements will be statistical analyzed separately for Parts A and B. The statistical analysis for the changes from baseline measurements will be used to test the primary hypothesis, while the statistical analysis for the percentage changes from baseline measurements will be used as a sensitivity analysis. A sequential stepwise hypothesis and a Hochberg testing procedure will be utilized to allow for multiple testing while preserving the overall significance level of the trial.

For Parts A and B separately a repeated measures ANCOVA will be used to compare the changes and percentage changes from baseline in daily insulin use between treatment groups for each timepoint. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1

Subject will be used as a random effect. The least squares (LS) mean for each treatment will be presented for each timepoint. Also, the difference between treatments, the 95% confidence interval (CI) of the differences, and p-value associated with the null-hypothesis of no difference will be reported for each timepoint where applicable based on the sequential testing methods as described below.

Step 1: The first step of the sequential testing will consist of a test for the effect of REMD-477. The Hochberg procedure will be used to assess the statistical significance of two tests: one for the superiority of 70 mg REMD-477 compared to placebo, the other for the superiority of 35 mg REMD-477 compared placebo. If the larger of the two p-values is less than the significance level (ie, 0.05), then both tests are considered to have reached statistical significance. Otherwise, if the smaller of the two p-values is less than half of the significance level (ie 0.025), then the corresponding test is considered to have reached statistical significance.

Step 2: If at least one of the two doses of REMD-477 is found to be superior to placebo, then the two doses of REMD-477 will be compared using the same significance level as that used to claim significance of either dose of REMD-477.

10.3.4.3 Fasting Glucose, MMTT and Arginine Challenge Test – Part A only

The following section applies to Part A only.

The fasting glucose concentrations, concentrations following the MMTT and Arginine Challenge Test (ACT), will be summarized by treatment group and timepoint, along with changes from baseline. The percentage changes from baseline for fasting glucose concentrations will also be summarized by treatment group and timepoint. Figures of mean profiles, changes and percentage changes from baseline will be presented by treatment. The baseline fasting glucose is the last value measured prior to the first study drug dosing. The MMTT baseline is the average value from the -10 minute and -1 minute timepoints for each MMTT. The ACT baseline is the 0 minute timepoint, which is equivalent to the 120 minute timepoint of the MMTT.

The difference in glucose concentration following MMTT will be derived as the glucose concentration at the 120 minute timepoint at MMTT, minus the MMTT baseline glucose concentration. This metric will be summarized by treatment group and study day, along with changes from baseline, where baseline is the defined as the metric obtained at the Lead-in (OBV) period for those subjects enrolled prior to amendment # 1 of the protocol or the baseline visit for those thereafter.

Concentrations of glucose, c-peptide, glucagon, insulin, GLP-1 (active and total) will be used to derive the respective AUC (unadjusted and adjusted by test baseline) from the MMTT and ACT for each study day.

AUC will be calculated using the linear trapezoidal method. To calculate AUC adjusted for baseline, the baseline concentration value will be subtracted from all post-test concentrations. Any negative values after baseline adjustment will be set to zero.

AUC calculations, where possible, will be carried out using actual post-dose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval. The baseline for AUC of each parameter is the value derived from the concentrations obtained at the Lead-In (OBV) period for those subjects enrolled prior to Amendment # 1 of the protocol or the baseline visit for those thereafter.

The change from baseline measurements for fasting glucose, the change from baseline difference in glucose concentration following MMTT, and the change from baseline of the derived AUC for glucose, C-peptide, glucagon, insulin and GLP-1 (active and total), unadjusted and adjusted by test baseline, will be statistically analyzed. The percentage change from baseline for the derived AUC, unadjusted and adjusted by test baseline for C-peptide, will also be statistically analyzed. A repeated measures ANCOVA will be used to compare the each of these parameter between treatment groups for each timepoint. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1

Subject will be used as a random effect. The LS mean for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be reported for each timepoint.

10.3.4.4 Continuous Glucose Monitoring and Seven-point Glucose Profile

The following mean and changes from baseline in parameters from the CGM and seven-point glucose profile assessment will be summarized separately for Parts A and B by treatment. For the Average Daily 24-h Glucose Concentration, the percentage changes from baseline will also be summarized separately for Parts A and B by treatment.

- Average Daily 24-h Glucose Concentration
    - Derived as the average 24-h glucose concentration, over the course of 7 days or 3 days, for CGM and seven-point glucose respectively.
- Time within Target Range (70-180 mg/dL), Time lower than Target Range (<70 mg/dL) and Time higher than Target Range (> 180 mg/dL)
    - Derived as the percentage of time for which the glucose concentration falls into these corresponding ranges, over the course of 7 days for CGM
    - Derived as the summation of time intervals where the glucose concentration falls into these corresponding ranges, divided by the total assessed time, and expressed as a percentage, for the seven-point glucose assessment.

The changes from baseline values will be statistically analyzed by part. For the Average Daily 24-h Glucose Concentration, the percentage changes from baseline will also be statistically analyzed by part. The baseline for CGM parameters is defined as the average value obtained from the Lead-In (Part A – 14 to 28 days; Part B – 7 to 14 days) period. The baseline for seven-point glucose is defined as the average obtained from the three consecutive days during the Lead-In (2 to 4 weeks) period.

A repeated measures ANCOVA will be used to compare the change from baseline values for the above parameters between treatment groups for each timepoint for Parts A and B separately. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1.

Subject will be used as a random effect. The LS mean for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be reported for each timepoint.

Although CGM will be conducted throughout the study from Dose 1 through EOS visit for safety monitoring and insulin use adjustments, the CGM data collected during the one week periods following Doses 4, 8, and 12 and during wash-out on Weeks 16 and 20 will be analyzed.

The ratio of average glucose obtained from the CGM at Day 78 (Week 12) and Baseline will be multiplied against the ratio of average daily insulin use obtained from the insulin diary at Day 78 (Week 12) and Baseline. This metric will be derived as described below and summarized by treatment.

$$\frac{Average\ Daily\ Glucose\ from\ CGM\ at\ Week\ 12}{Average\ Daily\ Glucose\ from\ CGM\ at\ Baseline} * \frac{Average\ Daily\ Insulin\ Use\ at\ Week\ 12}{Average\ Daily\ Insulin\ Use\ at\ Baseline}$$

For Parts A and B separately an ANOVA will be used to compare the values for the above metric between treatment groups. Dependent variables will be treatment. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1.

The LS mean for each treatment will be presented. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be produced.

10.3.4.5 Insulin, C-peptide, GLP-1 (active & total) and Glucagon

The insulin, C-peptide, GLP-1 (active & total) and glucagon concentrations will be summarized separately for Parts A and B by treatment group and timepoint, along with changes from baseline. Figures of parameter means and changes from baseline will be presented by treatment. The baseline assessment for Part A subjects is defined as the measurement taken at the Lead-In (OBV) period for those subjects enrolled prior to Amendment # 1 of the protocol or the baseline visit for those thereafter. For subjects enrolled in Part B the baseline assessment is defined as the last assessment taken prior to Day 1 dosing.

The respective change from baseline measurements for C-peptide, GLP-1 (active & total) and glucagon will be statistically analyzed for Part A subjects only. The respective change from baseline measurements for insulin will be statistically analyzed for Part A and B separately. A repeated measures ANCOVA will be used to compare each parameter between treatment groups for each timepoint. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1.

Subject will be used as a random effect. The LS mean for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be reported for each timepoint.

10.3.4.6 HbA1c

The HbA1c concentrations will be summarized separately for Parts A and B by treatment group and timepoint, along with changes from baseline. The baseline assessment for Part A subjects is defined as the measurement taken at the Lead-In (OBV) period for those subjects enrolled prior to Amendment # 1 of the protocol or the baseline visit for those thereafter. For subjects enrolled in Part B the baseline assessment is defined as the last assessment taken prior to Day 1 dosing..

The changes from baseline for HbA1c will be statistical analyzed separately for Parts A and B. A repeated measures ANCOVA will be used to compare changes between treatment groups for each timepoint. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate. Covariates may be added to the above model depending on the results from the comparison of baseline characteristics as detailed in section 10.3.4.1.

Subject will be used as a random effect. The LS mean for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be reported for each timepoint.

The number and proportion of subjects who achieve HbA1c reduction of $\geq$ 0.4% will be summarized separately for Parts A and B by timepoint and treatment group. Reduction of $\geq$ 0.4% is defined by the occurrence of a change from baseline which is less than -0.4%. A chi-square test will be conducted to compare the frequency observed in each of the two REMD-477 treatment groups versus the placebo group at each post-baseline timepoint.

10.3.4.7 Serum Ketones and Free Fatty Acids

The serum ketones and free fatty acids concentrations will be summarized by treatment group and timepoint, along with its changes from baseline. The baseline value for subjects in Part A enrolled prior to protocol amendment #1 is the average value between the Lead-In (OBV) period and Day 1 pre-dose. For all other subjects the baseline value is the last assessment taken prior to Day 1 dosing

10.3.4.8 Plasma Glucose from YSI – Part A only

Hourly plasma glucose results obtained from YSI will be listed.

10.3.4.9 Blood Ketones from Finger-Stick

Details of the blood ketones assessments which were captured in the eCRFs will be listed.

10.3.5 Exploratory Statistical Methodology

10.3.5.1 Body Weight

The body weight will be summarized separately for Parts A and B by treatment group and timepoint, along with changes from baseline and percentage change from baseline. Figures of mean body weight, its changes and percentage changes from baseline will be presented

separately for Parts A and B by treatment. The baseline assessment for Part A subjects is defined as the measurement taken at the Lead-In (OBV) period for those subjects enrolled prior to Amendment # 1 of the protocol or the baseline visit for those thereafter. For subjects enrolled in Part B the baseline assessment is defined as the last assessment taken prior to Day 1 dosing.

10.3.5.2 QOL Questionnaires

The results from the WHO-5 Well-Being Index and T1-DDS QOL Questionnaires will be summarized separately for Parts A and B by treatment group as frequency tables and listed.

10.3.5.3 Intrahepatic lipid content measured by MRI-PDFF

For a subset of Part B subjects the intrahepatic lipid content measured by MRI-PDFF will be summarised by treatment and timpoint and listed.

10.3.5.4 Intrahepatic lipid content measured by FibroScan

For a subset of Part B subjects the intrahepatic lipid content measured by FibroScan will be summarised by treatment and timpoint and listed.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse Events

A baseline sign and symptom is defined as an adverse event (AE) that starts after the subject has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs post-dose or that is present pre-dose and becomes more severe post-dose.

All AE listings and summaries will be presented separately for Parts A and B.

All AEs will be listed. The TEAEs will be summarized by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarized by treatment, and by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of probably or possibly related). Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

Onset times post-dose will be calculated from the last dose administered.

10.4.2 Clinical Laboratory Parameters

Biochemistry and hematology data will be summarized separately for Parts A and B by treatment. Changes from baseline will be calculated.

Values for any biochemistry, hematology, and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings.

AST, ALT, total and direct bilirubin will be summarized by treatment and timepoint. Changes from baseline will also be summarized.

The frequency of subjects who have a maximum ALT >3x ULN for any post-dose timepoint will be presented by treatment group. Additionally, the frequency of subjects who have an ALT > 3x ULN will also be presented for each assessment timepoint and treatment group. Similar tables shall also be presented for >5x ULN and >10x ULN. These frequency displays will also be provided for AST. The incidence of subjects who also have >3x ULN increases in ALT and/or AST with >2x ULN of total bilirubin will also be summarized by timepoint and treatment group.

A repeated measures ANCOVA will be used to compare the change from baseline in LDL cholesterol results between treatment groups on each day for Parts A and B separately. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate.

Subject will be used as a random effect. The LS means for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% confidence interval of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be for each day.

The SAS code will be similar to as shown below:

```
proc mixed data=xxx;
class subject day treatment;
model variable = baseline subject treatment day treatment*day;
repeated day / subject=subject type=csh;
lsmeans treatment*day / pdiff cl alpha=0.10;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

10.4.3 Vital Signs

The vital signs data (blood pressure, respiratory rate, pulse rate and body temperature) will be summarized separately for Parts A and B by treatment, together with changes from baseline (see Section 10.1.1 for definitions of baseline). Figures of mean vital signs and its changes from baseline will be presented by treatment.

A repeated measures ANCOVA will be used to compare the change from baseline in pulse rate and systolic and diastolic blood pressure results between treatment groups on each day for Parts A and B separately. Dependent variables will be treatment, day, and the treatment by day interaction. The baseline variable will be used as a covariate.

Subject will be used as a random effect. The LS means for each treatment will be presented for each timepoint. Also, the difference from placebo, the 95% confidence interval of the difference

from placebo, and p-value associated with the null-hypothesis of no difference will be for each day.

The SAS code will be similar to as shown below:

```
proc mixed data=xxx;
class subject day treatment;
model variable = baseline subject treatment day treatment*day;
repeated day / subject=subject type=csh;
lsmeans treatment*day / pdiff cl alpha=0.10;
ods output lsmeans=lsm;
ods output diffs=diff;
run;
```

10.4.4 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Bazett correction (QTcB), the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, heart rate, and RR.

The ECG data will be summarized separately for Parts A and B by treatment, together with changes from baseline (see Section 10.1.1 for definitions of baseline). Figures of mean ECG data and mean change from baseline profiles will be presented separately for Parts A and B by treatment. The relationship between plasma concentrations of REMD-477 and changes from baseline in QTcF and QTcB will be explored graphically.

An outlier analysis will be performed including all individual post-dose QTcF and QTcB measurements (not the mean data), including all repeat and unscheduled readings. The frequency of subjects with a maximum increase from baseline in QTcB and QTcF intervals will be summarized for each treatment according to the following categories: >30 to 60 ms, >60, and ≤30 ms. All incidences of >30 to ≤60 ms, and >60 ms will be flagged on the listing. In addition, the frequency of subjects with QTcB and QTcF post-dose values will be summarized for each treatment, according to the following categories: >450 to 480, >480 to 500, >500, and ≤450 ms. All incidences of >450 to 480, >480 to 500, and >500 ms will be flagged on the listing.

For Parts A and B separately the change from baseline of QT interval will be analyzed with a repeated measures ANCOVA. Dependent variables will be treatment, timepoint and the treatment by timepoint interaction. The change from baseline of the RR interval will serve as a covariate. Day is fitted as a repeated measure within subject. The estimated treatment means of the change from baseline of QT interval when change in RR interval equals zero will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be presented for each timepoint.

An example of the SAS codes (abbreviated) is shown below:

```
proc mixed data=xxx;
class subject day trtan;
```

```
model chg = chg_rr subject trtan day treatment*day;
repeated day / subject=subject type=csh;
lsmeans trtan*day / pdiff cl alpha=0.05;
estimate 'Est_CFB RR=0' intercept 1 chg_rr 0 trtan 1 0 avisit 1 0 0
trtan*avisit 1 0 0 0 0 0 /e;
…
run;
```

A similar analysis will be performed using the change from baseline in QTcF. Dependent variables will be treatment, timepoint, and the treatment by timepoint interaction. The baseline QTcF will serve as a covariate. Day is fitted as a repeated measure within subject. Treatment LS means will be presented for each timepoint. Also, the difference from placebo, the 95% CI of the difference from placebo, and p-value associated with the null-hypothesis of no difference from placebo, will be presented at each timepoint.

An example of the SAS codes is shown below:

```
proc mixed data=xxx;
class subject day trtan;
model chg = base subject trtan day treatment*day;
repeated day / subject=subject type=csh;
lsmeans trtan*day / pdiff cl alpha=0.05; run;
```

10.4.5 Incidence of Hypoglycemic Events

CGM will be conducted throughout the study from Dose 1 through EOS visit for safety monitoring and insulin use adjustments. The CGM data collected during this period will be analyzed separately for Parts A and B for the incidence of hypoglycemic events.

A hypoglycemic event is defined as an incident where the glucose value obtained from the CGM in a previous timepoint is higher than 70 mg/dL, but drops to 70 mg/dL or less in the subsequent timepoint with the low CGM glucose reading lasting at least 10 minutes. Each event will be counted even when multiple events occur on the same day, however if consecutive readings of GCM are deemed low then only a single event will be counted. The frequency of hypoglycemic events will be summarized by treatment group and timepoint (week). The categories for this frequency summary are as follows:

- Subjects with no hypoglycemic events
- Subjects with 1 to 5 hypoglycemic events
- Subjects with 6 to 10 hypoglycemic events
- Subjects with 11 to 15 hypoglycemic events
- Subjects with 16 or more hypoglycemic events

The same summary will be repeated for the second hypoglycemic threshold, where a hypoglycemic event is defined as an incident where the glucose value obtained from the CGM in

a previous timepoint is 54 mg/dL or higher, but drops below 54 mg/dL in the subsequent timepoint.

10.5 Pharmacokinetic Assessment

Plasma REMD-477 concentrations will be summarized separately for Parts A and B by the treatment group and listed for the PK population. REMD-477 concentrations were evaluated pre-dose on Days 1, 8, 29, 57, 85, and 106.

10.5.1 REMD-477 Antibody Assessment

Neutralizing and non-neutralizing antibody data will be listed separately for Parts A and B.

11 INTERIM ANALYSES

No formal interim analysis is planned; however, an unblinded preliminary analysis of the safety and pharmacodynamics data may be completed for internal business decisions and to help with planning future studies for REMD-477. This unblinded analysis may take place after the 30th and 60th subject enrolled in this study completes the Day 85 visit. Unblinding of subject treatment assignment will be limited to the designated unblinded Covance team and REMD study teams; Investigators and subjects will remain blinded. The unblinded team from Covance is separate to the study team that will be responsible to analyze the data post database lock.

The preliminary analyses may be shared with the Investigators in an aggregate form such that blinding is maintained.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

The product of the ratio of average glucose obtained from the CGM at Day 78 (Week 12) and Baseline; and the ratio of average insulin use obtained from the insulin diary at Day 78 (Week 12) and Baseline, were not statistically analyzed with repeated measures ANCOVA since this is not a metric assessed at multiple timepoints. The definition of a hypoglycemic event was updated after the 1st interim of Part A to be defined as an incident where the glucose value obtained from the CGM in a previous timepoint is higher than 70 mg/dL, but drops to 70 mg/dL or less in the subsequent timepoint with the low CGM glucose reading lasting at least 10 minutes.

Additional analysis of the LDL cholesterol data has been added.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.