Study Protocol Number: **R477-202**

Study Protocol Date: **26 October 2018**

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**

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

(Protocol No. R477– 202)

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Date: 03 April 2017

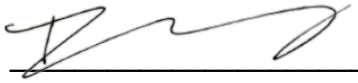
Amendment 1 29 May 2018

Amendment 2 26 October 2018

Declaration of Sponsor

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.

This clinical trial protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the Investigational Product, with moral, ethical, and scientific principles governing clinical research and in accordance with Good Clinical Practice and applicable federal and local regulations.



02 November 2018

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

Date

Investigator's Agreement

I have read the attached protocol entitled: 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, dated 26 October 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of REMD Inc.

_____

Signature

_____ _____

Name of Principal Investigator Date

Protocol Synopsis

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

Study Phase: 2

Indication: Type 1 Diabetes Mellitus (T1DM)

Primary Objective:

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

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 AUC after MMTT – Part A only.
- To compare the effects of a 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 a 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 area under the curve (AUC) after a mixed meal tolerance test (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.

Exploratory Objectives:

- To compare the effects of multiple doses of REMD-477 versus placebo on change from baseline at Week13 in body weight.
- To compare the effects of multiple doses of REMD477 versus placebo on change from baseline at week 13 in 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)

Hypothesis:

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

Study Design:

This is a randomized, placebo-controlled, double-blind study to evaluate the efficacy, safety, and pharmacodynamics (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.

This 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 arginine challenge will be examined. For subjects in Part A, alpha cell function will be assessed by measuring fasting glucagon, active and total glucagon-like peptide 1 (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 Baseline Overnight Visit (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.

Primary, Secondary, and Exploratory Endpoints:

Primary Endpoints:

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

Secondary Endpoints:

- Change from baseline at Week 13 in fasting glucose and glucose AUC after the MMTT – in 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).
- Subject incidence of adverse events and clinically relevant changes in medical history, physical examination, laboratory safety values, and ECGs.
- Incidence of hypoglycemic events.
- Change from baseline at Week 13 in HbA1c.
- Proportion of subjects who achieve HbA1c reduction of ≥ 0.4%.
- Change from baseline at 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) – Part A only.
- 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 challenge – Part A only.
- REMD-477 plasma concentrations and incidence of anti-REMD-477 antibody formation.

Exploratory Endpoints:

- Change from baseline at Week 13 in body weight.
- Change from baseline in QOL score at Week 13.
- Changes in intrahepatic lipid content as measured by magnetic resonance imaging – proton density fat fraction (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).

Sample Size:

Approximately 150 subjects (75 in Part A and 75 in Part B) with T1DM will be enrolled in this study and randomized in a 1:1:1 fashion to placebo, 35 mg REMD-477, or 70 mg REMD-477.

Summary of Subject Eligibility Criteria:

The following criteria apply to all subjects to be enrolled:

Inclusion Criteria:

1. Men and women between the ages of 18 and 65 years old, inclusive, at the time of screening;
2. Females of non-child bearing potential must be ≥1 year post-menopausal (confirmed by a serum follicle-stimulating hormone (FSH) levels ≥ 40 IU/mL) or documented as being surgically sterile. Females of child bearing potential must agree to use two methods of contraception during the entire study and for an additional 3 months after the end of the dosing with the investigational product;
3. Male subjects must be willing to use clinically acceptable method of contraception during the entire study and for an additional 6 months after the end of the treatment period;
4. Body mass index between 18.5 and 32 kg/m^2, inclusive, at screening (note that the subject's total daily insulin should be $\leq$ 1.0 unit/kg);
5. Diagnosed with Type 1 diabetes, based on clinical history or as defined by the current American Diabetes Association (ADA) criteria;
6. HbA1c > 7% and < 10% at screening;
7. Fasting C-peptide < 0.7 ng/mL;
8. Treatment with a stable insulin regimen for at least 8 weeks before screening with multiple daily insulin (MDI) injections or continue subcutaneous insulin infusion (CSII)
9. Willing to use study-dedicated Continuous Glucose Monitoring (CGM) system (e.g. DexCom) throughout the study; subjects may continue to use personal CGM systems during the study but must be on stable use for at least 3 months prior to screening.
10. ALT and/or AST ≤ 1.5x ULN at screening;
11. Able to provide written informed consent approved by an Institutional Review Board (IRB).

Exclusion Criteria:

1. History or evidence of clinically-significant disorder or condition that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion;

2. Significant organ system dysfunction (e.g., clinically significant pulmonary or cardiovascular disease, anemia [Hemoglobin < 10.0 g/dL], known hemoglobinopathies, and renal dysfunction [eGFR < 60 ml/min]);
3. Any severe symptomatic hypoglycemic event associated with a seizure or requiring help from other people or medical facility in the past 6 months;
4. Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident ≤12 weeks before screening;
5. History of New York Heart Association Functional Classification III-IV cardiac disease;
6. Current or recent (within 1 month of screening) use of diabetes medications other than insulin – subjects on an SGLT2 inhibitor should discontinue the SGLT2 inhibitor during the Screening Period, at least 2 weeks prior to the start of the Lead-in Period;
7. Use of steroids and/or other prescribed or over-the-counter medications that are known to affect the outcome measures in this study or known to influence glucose metabolism;
8. Smokes > 10 cigarettes/day, and/or is unwilling to abstain from smoking during admission periods;
9. Known sensitivity to mammalian-derived drug preparations, recombinant protein-based drugs or to humanized or human antibodies;
10. History of illicit drug use or alcohol abuse within the last 6 months or a positive drug urine test result at screening;
11. History of pancreatitis, pancreatic neuroendocrine tumors or multiple endocrine neoplasia (MEN) or family history of MEN;
12. History of pheochromocytoma, or family history of familial pheochromocytoma;
13. Known or suspected susceptibility to infectious disease (e.g. taking immunosuppressive agents or has a documented inherited or acquired immunodeficiency);
14. Known history of positive for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HbsAg), or hepatitis C antibodies (HepC Ab);
15. Participation in an investigational drug or device trial within 30 days of screening or within 5 times the half-life of the investigational agent in the other clinical study, if known, whichever period is longer;
16. Blood donor or blood loss > 500 mL within 30 days of Day 1;
17. Women who are pregnant or lactating/breastfeeding;
18. Unable or unwilling to follow the study protocol or who are non-compliant with screening appointments or study visits;
19. Any other condition(s) that might reduce the chance of obtaining study data, or that might cause safety concerns, or that might compromise the ability to give truly informed consent.

Investigational Product Dosage and Administration:

REMD-477 will be supplied as single-use glass vials and formulated with 10 mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20 at a protein concentration of 70 mg/mL. Placebo will be supplied as single-use glass vials and formulated with 10 mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20. All REMD-477 and placebo injections will be given in the same volume for all subjects.

REMD-477 and placebo will be administered by SC injections to the subject's anterior abdominal wall.

This will be a randomized, double-blinded, placebo-controlled study. All subjects and study staff, except for the study pharmacist and the biostatistician (who prepares the randomization schedule), will be blinded to the study treatments to be given to the subjects.

Study Procedures:

All study specific procedures and visits are shown in Appendix A.

Screening Visit:

All experimental procedures will be explained in writing and orally to the subject by the principal investigator, co-investigator, or appropriate research staff. The objectives of the project, all of the requirements for participation, and any possible discomforts and risks will be clearly explained to each subject orally and in writing in lay terms that he/she is able to comprehend. The subject must sign an IRB-approved informed consent form before participating in any aspect of the study.

A medical examination, including medical history and physical examination, hematology and blood chemistry, urine tests, a 12-lead ECG, and other screening tests will be performed as per the Schedule of Assessments.

Lead-In Period:

The Lead-in Period applies to all subjects and may begin when a subject is judged by an investigator to be eligible, after the initial screening. For subjects participating in Part A, the Lead-In Period may last between 2 and 4 weeks. For subjects participating in Part B, the Lead-in Period may last between 1 and 2 weeks. The subject will be given a DexCom CGM and Subjects in Part A will be required to wear it for a minimum duration of two weeks prior to the **Baseline Visit**, while subjects in Part B will be required to wear it for a minimum duration of 1 week prior to the **Day 1 Visit**. Insulin treatment will continue, and the subject will be given an insulin usage diary. Assessments of daily insulin use (short-acting, long-acting, and infusional, as applicable) will be recorded over a 14 day period prior to the Baseline Visit for subjects in Part A, or over a 7 day period prior to the Day 1 Visit for subjects in Part B. During the Lead-In Period, subjects will also record their blood glucose levels in a seven-point glucose profile over a single period of 3 consecutive days either, prior to the Baseline Visit (subjects in Part A) or prior to the Day 1 Visit (subjects in Part B).

Overnight Baseline Visit (OBV): *Day -8/-7 to Day -2/-1 (applies to a subset of subjects in Part A who were enrolled prior to Protocol Amendment #1)*

After the Lead-in Period (which includes the completion of the two week CGM period), eligible subjects will be admitted to the CRU around 4:00 pm for a single overnight stay on one of the following study days: Day -8, -7, -6, -5, -4, -3, or -2 relative to the subject's scheduled dosing day (Day 1). The OBV must be performed within 8 days (check-in to occur between Day -8 to Day -2) prior to administration of study drug.

At the time of admission, data from the DexCom CGM device, the subject's diary capturing insulin use, and the seven-point glucose measurements will be obtained and reviewed. CGM results from the study DexCom device will be downloaded and typical measures of glycemic control (mean glucose, standard deviation, time in range) will be recorded. CGM results will be unblinded throughout the study.

Additionally, the following baseline assessments will be completed: medical history, physical exam, body weight, urine pregnancy test, urine drug and alcohol test, 12-lead ECG, and vital signs, per the Schedule of Assessments. Safety and PD labs, including serum chemistry, hematology, urinalysis, HbA1c, insulin, C-peptide, glucagon, serum ketones, free fatty acids (FFA), and GLP-1 will be collected. Fasting plasma glucose samples will be collected on the following morning, prior to the administration of the MMTT and Arginine Challenge Tests. During the 8 hour overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia.

For subjects on insulin pumps: Subjects will be admitted to the CRU at approximately 1600 (4:00 pm). A peripheral IV will be placed at this time. They will be given a standard dinner at 1800 (6:00 pm) for which they can bolus as they normally would via their insulin pump for that particular meal. At approximately 1900 (7:00 pm), the subject's insulin pump will be disconnected and suspended and IV insulin infusion will begin. Blood glucose control will be maintained per Appendix C to maintain euglycemia in the 90-120 mg/dl range with start rates

described in Appendix C. The MMTT and arginine challenge will then be performed the next morning at approximately 8:00 am [please note: the insulin infusion will continue until the completion of the both the MMTT and Arginine Challenge Test assessments]. After completing the 2 hour MMTT, subjects will be administered an arginine challenge test. During both challenge tests, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia. Upon completion of all tests, subjects may be given additional insulin via SC injection or a bolus of insulin via either IV or insulin pump, at the discretion of the investigator. Additionally, the subject's insulin pump will be restarted immediately after completion of all tests. Subjects will be monitored closely by CGM and YSI as needed and discharged only after blood glucose is < 250mg/dl and relatively stable (not rapidly declining).

For subjects on insulin injections with basal insulin given at night: Subjects can take their last dose of long acting insulin 1 day prior to admission in the evening. They will be admitted and be administered SC or bolus insulin as they would with their rapid acting injection for dinner. Insulin infusion via IV will start at 7:00 pm. No basal insulin injection will be given SC on the night of admission. After all study procedures have been completed the next morning, subjects may receive additional insulin via SC injection or an IV bolus, at the discretion of the investigator. At that time, they should take half their normal dose of basal insulin SC. They can take the second half at their usual time later that evening. The following day, they can resume their full, normal basal insulin dose.

For subjects on insulin injections with basal insulin given in the morning: Subjects will take their normal AM dose of basal insulin on the morning of the day of admission. They will be admitted, and be administered SC or bolus insulin as they would with their rapid acting injection for dinner. IV insulin will be started at 7:00 pm. Of note, given that subjects will have their basal insulin working overnight, they will likely require much less IV insulin, and thus per Appendix C will be started on a much lower infusion rate. After all study procedures have been completed the next morning, the subject may receive additional insulin either via SC injection or an IV bolus (at the discretion of the investigator), and subjects will take their regular dose of basal insulin. The following day, they can resume their dose in the morning as they usually would.

Baseline Visit: *(applies to subjects in Part A who are enrolled at the time of Protocol Amendment #1)*

After the Lead-in Period (which includes the completion of the two week CGM period), eligible subjects will return to the CRU, after completing an 8 hour overnight fast at home, on the morning of one of the following study days: Day -8, -7, -6, -5, -4, -3, -2 or -1 relative to the subject's scheduled dosing day (Day 1). For subjects who are enrolled at the time of this Protocol Amendment, overnight admission to the CRU will not occur.

At the beginning of the visit, data from the DexCom CGM device, the subject's diary capturing insulin use, and the seven-point glucose measurements will be obtained and reviewed. CGM results from the study DexCom device will be downloaded and typical measures of glycemic control (mean glucose, standard deviation, time in range) will be recorded. CGM results will be unblinded throughout the study.

Additionally, the following baseline assessments will be completed: medical history, physical exam, body weight, urine pregnancy test, urine drug and alcohol test, 12-lead ECG, and vital signs, per the Schedule of Assessments. Safety and PD labs, including serum chemistry, hematology, urinalysis, HbA1c, insulin, C-peptide, glucagon, serum ketones, free fatty acids (FFA), and GLP-1 will be collected. Fasting plasma glucose samples will also be collected, prior to the administration of the MMTT. For all subjects, fasting blood glucose should be 80-180 mg/dl. During the overnight fasting at home, subject can drink juice or take glucose tabs if hypoglycemic. No rapid acting insulin should be taken within 4 hours prior of the MMTT. During the MMTT, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia.

For subjects on insulin pumps: The insulin pump will continue until the completion of the MMTT.

For subjects on insulin injections with basal insulin given at night: Subjects can take their last dose of long acting insulin in the evening prior to the Baseline Visit.

For subjects on insulin injections with basal insulin given in the morning: Subjects will take their normal AM dose of basal insulin in the morning a day prior to the Baseline Visit, as well as on the morning of the MMTT.

Upon completion of all tests, subjects may be given additional insulin via SC injection or a bolus of insulin via either IV or insulin pump, at the discretion of the investigator. Subjects will be monitored closely by CGM as needed and discharged only after blood glucose is < 250 mg/dl and relatively stable (not rapidly declining).

Note: *Neither the Overnight Baseline Visit (OBV) nor the Baseline Visit (BV) apply to subjects enrolled in Part B.*

Randomization and Day 1 Treatment for Subjects Enrolled in Part A: Week 1

On the morning of Day 1, eligible subjects will return to the CRU and will be randomized to placebo or REMD-477 at 35 mg or 70 mg, and undergo pre-dose safety, laboratory, and PD measurements as outlined in the Schedule of Assessments.

After completion of the pre-dose Day 1 tests and procedures, subjects will be administered study drug by SC injection. Upon completion of post-dose procedures, subjects will be discharged from the CRU when the Investigator feels that the subject's condition is stable.

Subjects will also be given the "Week 1" insulin usage diary to record daily insulin use. For Week 1, assessment of daily insulin use will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days. To

mitigate a potential risk of hypoglycemia, subjects with HbA1C ≤ 8.0% at screening, at the discretion of the investigator, may reduce their total insulin dose by 10-20% on the day of randomization. Hypoglycemia of different magnitudes will be evaluated via CGM. For this study, the primary threshold for hypoglycemia will be set at ≤ 70 mg/dl and second threshold at < 54 mg/dL.

Baseline, Randomization and Day 1 Treatment for Subjects Enrolled in Part B: *Week 1*

After the Lead-in Period (which includes the completion of the one week CGM period), eligible subjects will return to the CRU and will be randomized to placebo or REMD-477 at 35 mg or 70 mg. Prior to being dosed, the subject will undergo all pre-dose safety, laboratory, and PD measurements as outlined in the Schedule of Assessments, as these will serve as the subject's baseline.

After completion of the pre-dose Day 1 tests and procedures, subjects will be administered study drug by SC injection. Upon completion of post-dose procedures, subjects will be discharged from the CRU when the Investigator feels that the subject's condition is stable.

Subjects will also be given the "Week 1" insulin usage diary to record daily insulin use. For Week 1, assessment of daily insulin use will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days. For this study, the primary threshold for hypoglycemia will be set at ≤ 70 mg/dl and second threshold at < 54 mg/dL.

For Dose 2 through Dose 12: *Week 2 through Week 12*

Subjects will return to the CRU on an outpatient basis to receive weekly SC injections of REMD-477 or placebo for a total of 12 injections. Follow-up phone calls by the research staff will occur 3-4 days after Dose 1 and Dose 2 to assess subject insulin use and glucose control and to coach the subject on insulin dosing as needed to minimize hypoglycemia. Safety, PK, and PD assessments will be conducted on an outpatient basis at various time points as described in the Schedule of Assessments. These assessments will include physical exam, body weight, urinary pregnancy test (women), urine drug and alcohol test, 12-lead ECG, vital signs, serum chemistry, hematology, urinalysis HbA1c, insulin, C-peptide, glucagon, GLP-1, serum ketones, free fatty acids, REMD-477 serum concentrations, and fasting glucose (subjects should be instructed to fast overnight for 8 hours prior to collection). For subjects enrolled in Part B, additional safety assessment will include blood collection for liver injury biomarkers at timepoints outlined in the Schedule of Assessments – Part B.

Subjects will be given an insulin usage diary at the beginning of Weeks 2 through 4 to record daily insulin use. For Weeks 2 through 4, assessments of the daily insulin requirements will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days.

Subjects will also be given an insulin usage diary at the beginning of Weeks 8 and 12. For these weeks, assessments of daily insulin use will be obtained by taking the average total daily insulin

dose (short-acting, long-acting, and infusional as applicable) over a period of three consecutive days within that respective week.

Follow-up and End of Study (EOS): *Week 13 through Week 24*

Subjects receiving all 12 doses will be followed for 12 weeks after the last dose and will complete study evaluations as described in the Schedule of Assessments.

At Week 13 (1 week after receiving Dose 12) and Week 24 (End of Study Visit), a subset of subjects in Part A enrolled prior to Protocol Amendment #1, will be admitted to the CRU to complete an MMTT and arginine challenge test, after an overnight fast of at least 8 hours in a similar manner as done at the Overnight Baseline Visit. During the 8 hour overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia. During both challenge tests, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia.

For ongoing or newly enrolled subjects participating in Part A at the time of Protocol Amendment #1, overnight admission to the CRU on Week 13 and Week 24 will not occur. For these visits, subjects will return to the CRU to complete all the study procedures outlined in the Schedule of Assessments table – however, all assessments for that visit will be performed on a single day (i.e., the Week 13 Visit will be performed on Day 85, and the Week 24 Visit will be performed on Day 162).

For subjects enrolled in Part A:

- **Please Note:** For ongoing or newly enrolled subjects in Part A at the time of Protocol Amendment #1, the MMTT will only be administered at the Baseline and Week 13 visits, after the subject completes an 8 hour overnight fast at home (the MMTT is no longer required at Week 24). No Arginine Challenge Tests or YSI assessments will be performed for these subjects.

For subjects enrolled in Part B:

- **Please Note:** Neither the MMTT assessment nor Arginine Challenge Test assessment will be conducted.

Subjects will also be given an insulin usage diary at the beginning of weeks 16 and 20.

For these weeks, assessments of the daily insulin requirements will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) over a period of three consecutive days within that respective week.

Subjects who early terminate from the study during the 12-week treatment period will be monitored for 12 weeks after the last injection of study drug (REMD-477 or placebo).

Throughout the Study: Day 1 through End of Study

Subjects will be instructed to titrate their basal insulin dose to achieve a pre-breakfast blood glucose level of 4.4-6.6 mmol/L (80-120 mg/dL) and to titrate their bolus insulin dose to achieve a pre-lunch, pre-dinner, and bedtime blood glucose level of 4.4-6.6 mmol/L (80-120 mg/dL). Algorithms for titrating basal and bolus insulin doses to achieve target glycemic goals will be provided. The subjects' basal and bolus doses may be also adjusted at the discretion of the investigator's typical standard of care.

Adverse events and concomitant medications (including non-prescription medications and/or supplements such as protein / amino acid supplements) will be collected throughout the study when reported. Any rescue medications and use of meals/food to manage hypoglycemic sensations or events will be reviewed carefully with the subject and recorded accordingly. If there is a clinically significant laboratory abnormality or adverse event in need of monitoring, subjects will be followed until resolution of the abnormality or adverse event or until it is considered stable.

For subjects enrolled in Part A, CGM data will be collected throughout the study from Dose 1 through the End of Study Visit, and CGM devices will be "unblinded". For on-going or newly enrolled subjects in Part A at the time of Protocol Amendment #2, CGM data will be collected throughout the study from Dose 1 through the Day 85/Week 13 Visit, and CGM devices will be "unblinded". For subjects enrolled in Part B, CGM devices will be configured in a "blinded" fashion, wherein CGM data will not be accessible to the subject or the Investigator, and will be collected for one week intervals during specified time periods noted in the Schedule of Assessments – Part B (study weeks 1, 4, 8, and 12, after receiving that week's assigned dose).

Seven-point blood glucose profiles (measuring glucose via finger stick, at the following times of day: before each meal, 2 hours after each meal, and at bedtime) will be performed for periods of three consecutive days. During the Lead-In Period, subjects will record their seven-point blood glucose (BG) profile over a single period of three consecutive days, prior to the Baseline Visit for subjects enrolled in Part A, or prior to the Day 1 Visit for subjects enrolled in Part B. During the 12 week Dosing Period and 12 week Follow-up Period, seven-point BG profiles will be performed over the three consecutive days following Dose 4 (Study Days 23 – 25), Dose 8 (Study Days 51 – 53), and Dose 12 (Study Days 79 – 81), and during Weeks 16 and 20 of the Follow-up Period.

Subjects will be provided with a blood ketone meter and blood ketone test strips in order to measure blood ketone readings via finger-stick method. For subjects enrolled in Part A only, blood ketone readings will be performed in the morning and collected by the subject while in a fasted state, prior to the subject's morning meal. During the 12-Week Dosing Period (starting on Day 1 and continuing through the completion of Week 12) the blood ketone readings will be performed 3 days a week – on an alternate day basis starting on Day 1 (e.g. Week 1: Study Days 1, 3, 5 or on Mondays, Wednesdays, and Fridays), and once weekly during the 12-Week Follow-up Period. Subjects will be instructed to contact the investigator if they have positive ketones and blood sugars > 300 mg/dL. Subjects enrolled in Part B will also be provided with a blood ketone meter and blood ketone test strips to be used as needed, however, there is no

required collection schedule. Subjects in Part B will be advised to perform blood ketone readings via finger-stick method when they feel ill, or symptomatic of ketoacidosis, or as instructed by the investigator.

The Type 1 – Diabetes Distress Scale (T1-DDS) and WHO-5 Well-Being Index scales (Appendix D) will be provided to the subject at the beginning of the following study visits: Baseline Visit and Day 85 and Day 161(EOS) visits.

PK blood samples and fasting plasma glucose samples will be collected as described in the Schedule of Assessments. For those samples that are scheduled for collection on days when study drug is administered, those samples should be collected pre-dose.

Anti-REMD-477 antibody samples will be collected pre-dose on Days 1, 85, and at the End of Study Visit (Day 162).

For a subset of subjects enrolled 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. Also, blood samples to measure biomarkers of liver injury will be collected from Part B subjects on Day 1 (pre-dose), Day 29 (Week 5) , Day 57 (Week 9), Day 85 (Week 13), and Day 106 (Week 16).

Statistical Considerations:

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 group. Based on 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.

An analysis of variance will be used to evaluate pre to post intervention changes in daily insulin use.

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.

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, 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, then the corresponding test is considered to have reached statistical significance.

Step 2: If at least 1 of the 2 doses of REMD-477 is found to be superior to placebo, then the

2 doses of REMD-477 will be compared using the same significance level as that used to claim significance of either dose of REMD-477.

Preliminary analyses of variance will be performed to confirm that baseline characteristics of participants are similar in the groups. If necessary, analyses of covariance to adjust for any pre-intervention difference between groups will be performed. 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.

Descriptive statistics will be provided for selected demographics, safety and PD data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

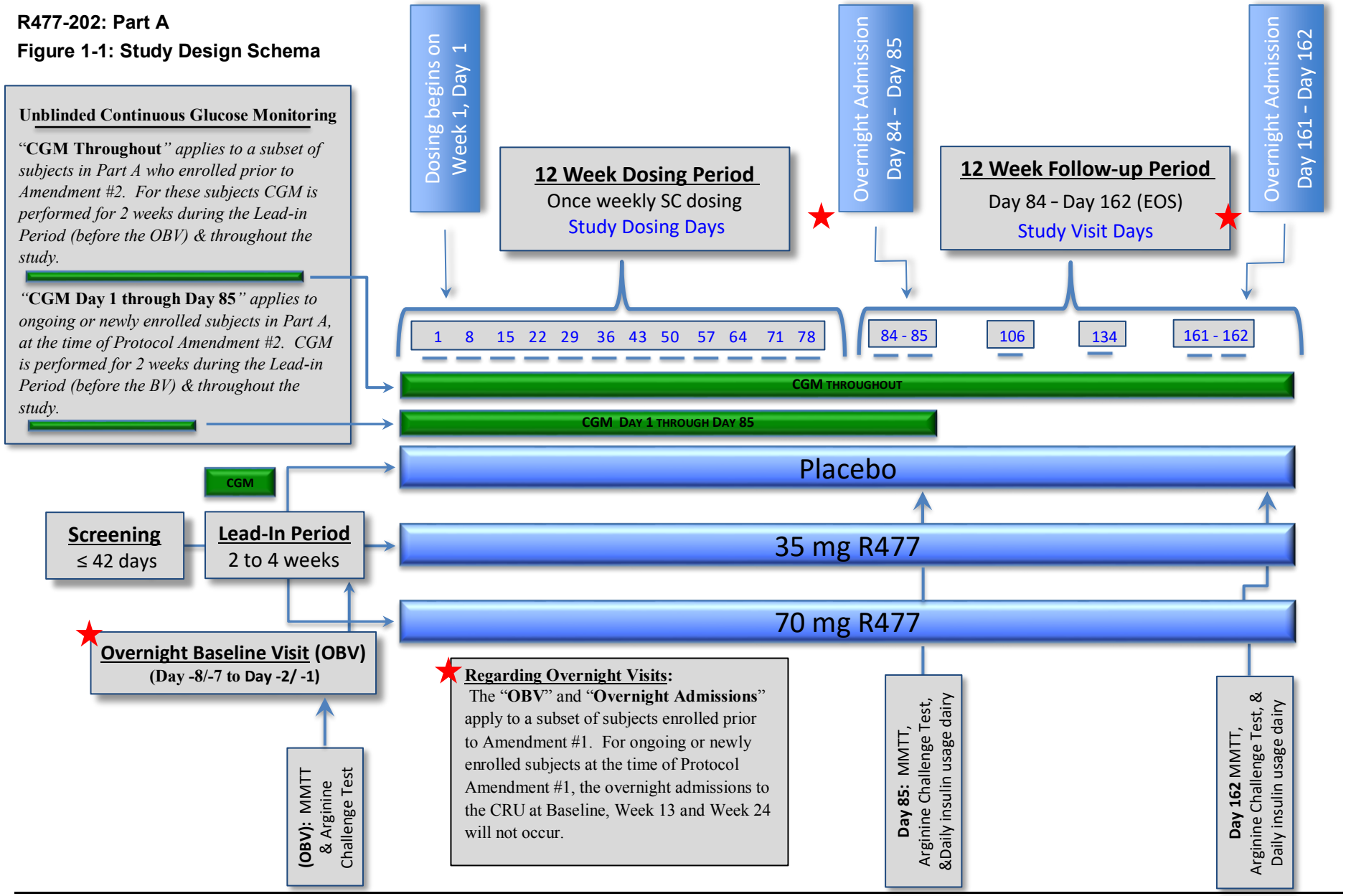
For the product of the ratio of average glucose (Week 12/Baseline) and ratio of average insulin use (Week 12/Baseline), glucose AUC after MMTT, C-peptide AUC after MMTT and arginine challenge test, fasting glucose, insulin, C-peptide, GLP-1, and glucagon, a repeated measures analysis of covariance will be performed, as well as before and after treatment analysis.

For comparison of proportion of subjects that achieve HbA1c reduction of ≥ 0.4% in the REMD-477 and placebo groups, chi-square test will be conducted.

Table of Contents

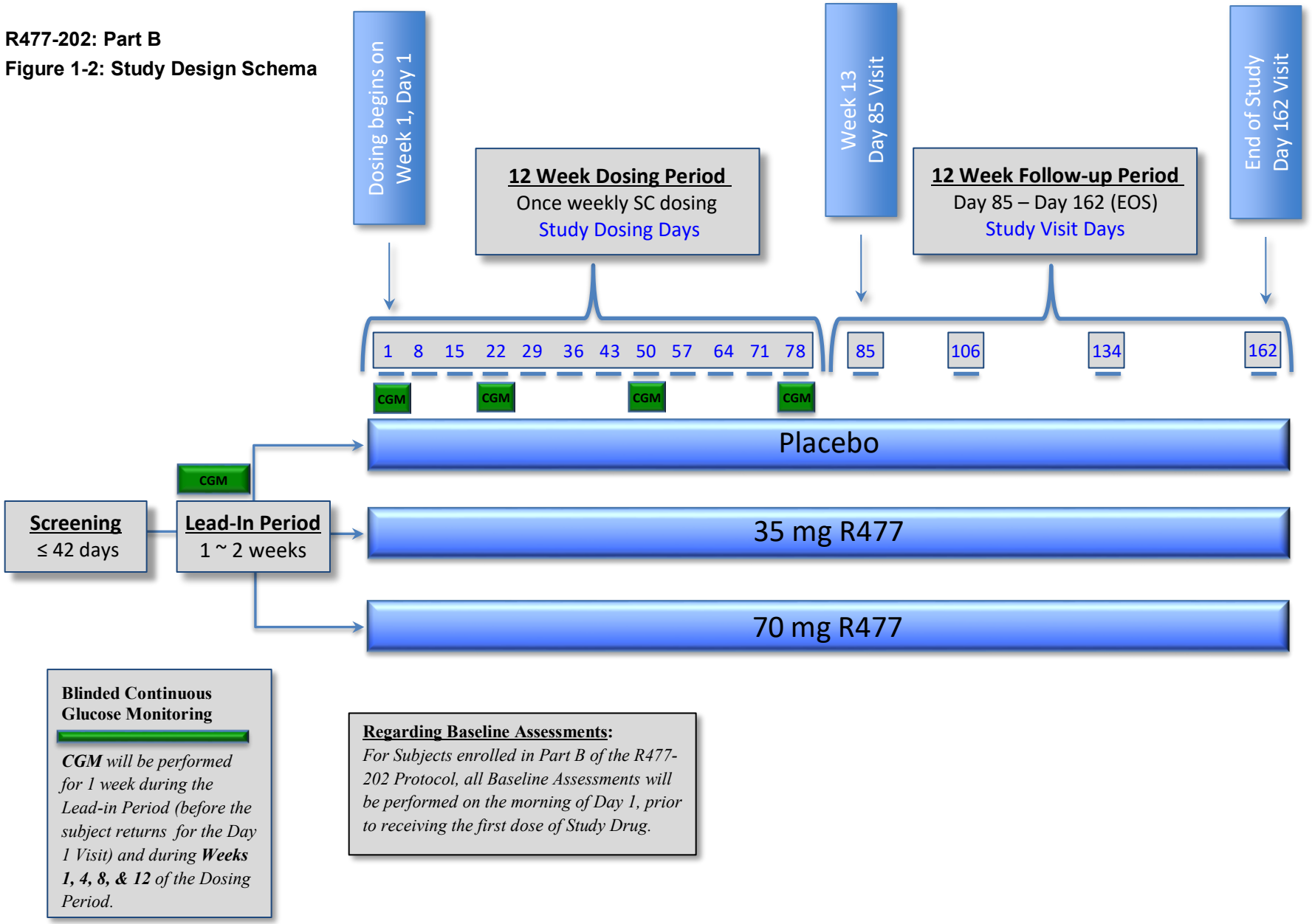
R477-202: Part A

Figure 1-1: Study Design Schema



R477-202: Part B

Figure 1-2: Study Design Schema



Study Glossary

Abbreviation or Term	Definition/Explanation
AE(s)	adverse event(s)
ADA	American Diabetes Association
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
BMI	body mass index
CGM	continuous glucose monitor
C_{max}	maximum observed concentration
CMO	contract manufacturing organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CTCAE	common terminology criteria for adverse events
eCRF	electronic case report form
ECG	electrocardiogram
EOS	end of study
FFA	free fatty acid
FIH	first-in-human
FSH	follicle-stimulating hormone
GCGR	glucagon receptor
GCP	good clinical practices
GLP-1	glucagon-like peptide 1
HbA1c	hemoglobin A1c
HbsAg	hepatitis B surface antigen
HepC Ab	hepatitis C antibodies
HIV	human immunodeficiency virus
ICF	Informed Consent Form
IRB	institutional review board
LFT	liver function test
MEN	multiple endocrine neoplasia
MMTT	mixed meal tolerance test
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
MRT	mean residence time
MTD	maximum tolerated dose
NOAEL	no observed adverse event level
OBV	overnight baseline visit
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
QRS	QRS complex in ECG recording
QTc	QT interval (corrected)
REMD	REMD Biotherapeutics Inc.
REMD-477	A glucagon receptor antibody developed by REMD
SC	Subcutaneous
T1DM	Type 1 diabetes mellitus
ULN	upper limit of normal

1. OBJECTIVES

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.

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 AUC after MMTT – in Part A only.
- To compare the effects of a 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 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 an MMTT and arginine challenge test (for a subset of subjects who were enrolled prior to Protocol Amendment #1) – in 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 – in Part A only.
- To determine REMD-477 plasma concentrations and formation of anti-REMD-477 antibodies after multiple dosing.

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 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)

2. BACKGROUND AND RATIONALE

Type 1 Diabetes

Diabetes is a growing health concern worldwide. Globally, as of 2010, an estimated 285 million people had diabetes, with type 1 making up about 10% of the cases (Williams textbook of endocrinology 12th edition). In 2013, an estimated 381 million people globally had diabetes (Int Diab Federation, 2015). By 2030, this number is estimated to almost double (Wild, 2004). In 2012, 29.1 million Americans, or 9.3% of the population, had diabetes, and approximately 1.25 million American children and adults have type 1 diabetes (National Diabetes Statistics Report, 2014).

Type 1 diabetes mellitus (previously known as insulin-dependent, juvenile or childhood-onset) results from autoimmune destruction of the insulin-producing beta cells in the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger) and weight loss (Cooke, 2008). Type 1 diabetic patients rely on insulin injections to control blood glucose.

Optimal blood glucose control in T1DM requires insulin in amounts that far exceed the endogenous insulin secreted by normal β-cells (Unger, 2010; Wang, 2013). A recent large scale observational study in 33,915 patients with T1DM, based on the Swedish National Diabetes Register (data of Jan 1998 - Dec 2011), showed that insulin treated T1DM patients had a significantly elevated risk of death due to cardiovascular diseases (death rate 2.7% vs. 0.9%) in comparison to the age-, sex-, and county-matched controls from the general public (Lind, 2014). Even among patients with better glycemic control (glycated hemoglobin ≤ 6.9%) and reduced diabetes-related death, there is still a nearly two-fold increase (1.7% vs. 0.9%) in cardiovascular disease related death, in comparison to the general public controls. Other studies reported 6-10 fold greater mortality related to coronary heart disease (CHD) in T1DM patients (Dorman, 1984; Korlewski, 1987). Two more studies, the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study (Orchard, 2003) and Eurodiab Study (Soedamah-Muthus, 2004), confirmed significant increases in the Coronary Artery Disease (CAD)-related mortality in T1DM. Hyperinsulinemia is known to increase hepatic cholesterol and triglyceride synthesis through insulin-mediated up regulation of lipogenic and cholesterogenic transcription factors such as SREBP and enzymes (Brown, 2008), contributing to CAD or CHD.

Relative or absolute insulin excess is also associated with a prominent risk of hypoglycemia and sudden death in T1DM patients. Hypoglycemia is a common side effect of insulin therapy, and a fact of daily life, for people with T1DM (Cryer, 2010). The current clinical guidelines call for tighter glycemic control, to prevent diabetic complications, but such practice is associated with higher incidence of iatrogenic hyperinsulinemia and hypoglycemia. T1DM patients also suffer asymptomatic hypoglycemia. In one study of T1DM patients with subcutaneous glucose sensing, glucose levels were below 70 mg/dL for 1.5 hours per day, i.e., 6.3% of the time (Beck, 2009). In another study of nocturnal plasma glucose measurements every 15 minutes, hypoglycemia (glucose <70 mg/dL) was found in 57% (12 of 21) of the T1DM patients (Raju, 2006). Asymptomatic hypoglycemic episodes are not benign as they desensitize and impair the physiological defenses against subsequent hypoglycemia (Cryer, 2010). People with T1DM suffer an average of two episodes of symptomatic hypoglycemia per week, and thousands of such attacks over a lifetime of diabetes. They also suffer an average of one severe episode of temporarily disabling hypoglycemia per year, which can be life-threatening.

Glucagon Receptor Pathway in Type 1 Diabetes

Glucagon is the primary counter-regulatory hormone that opposes insulin action. Normal β-cells secrete insulin, which restrains glucagon release from the juxtaposed α-cells. However, in absence of intra-islet insulin, such as the case of type 1 diabetes, α-cells are unrestrained and glucagon secretion is unopposed. Data from a series of studies have demonstrated that an increase in glucagon in patients with type 1 diabetes is a key component of the pathogenesis of hyperglycemia; 1) hyperglucagonemia is a prominent feature of both type 1 and 2 diabetes; 2) glucagon increases circulating glucose levels by stimulating hepatic gluconeogenesis and glycogenolysis; 3) the glucagon suppressors, leptin and somatostatin, can suppress all catabolic manifestations of diabetes during total insulin deficiency; 4) total β-cell destruction fails to induce diabetes in glucagon receptor (GCGR) knockout mice; and 5) perfusion of normal pancreas with anti-insulin antisera causes marked hyperglucagonemia (Unger, 2012). Recently, treatment with a glucagon receptor antagonist in a rodent model of T1D (Zhi, 2013) and in patients with T1D (Garhyan, 2013) found this therapy decreased insulin requirements.

Lack of insulin also leads to an unrestrained action of glucagon on the liver, which in turn unleashes the full capacity of the liver in glucose output and in ketone production. It has been reported that in insulin deficient animal models of diabetes, the metabolic

manifestations of insulin deficiency will not occur after GCGR knockout (Lee, 2012), and that insulin-deficient diabetes induced by streptozotocin injection, presented with severe hyperglycemia (>500 mg/dL), hyperketonemia, and fatal cachexia, can be prevented by GCGR knockout in mice (Lee, 2011).

It should also be noted that in clinical practice of treating T1DM, the exogenous insulin treatment can only attain the intra-islet insulin concentration at a small fraction of that achieved by the endogenous insulin. Therefore, glucagon hypersecretion and hyperactivity in T1DM cannot be adequately controlled by the exogenous insulin injections (Unger, 2012). These conditions predispose the type 1 diabetic patients to a metabolically vulnerable state, subjecting to poor diabetic control and risk of ketoacidosis.

The glucagon pathway has been contemplated as a therapeutic target in recent years. There have been some efforts in developing glucagon antagonists, including antibodies, but with little success even in preclinical settings. Antagonism to the GCGR is also being sought as a potential target, with small molecular antagonists being developed by a few pharmaceutical companies (Kazda, 2014; Vajda, 2014; Petersen, 2001).

While insulin remains a primary treatment for type 1 diabetes, its clinical utility and benefits are undermined by the undesirable iatrogenic hyperinsulinemia with associated cardiovascular and hypoglycemic complications. It is highly desirable to develop a safe and effective adjunct therapy that can substantially reduce the daily insulin doses. In contrast to the treatment of type 2 diabetes using a big range of therapeutic strategies, the treatment of type 1 diabetes places a heavy reliance on insulin with few choices for alternatives or add-ons. An effective and safe therapeutic alternative is badly needed to supplement and reduce insulin daily doses. This will substantially improve the diabetic control and life quality of the type 1 diabetic patients, and minimize iatrogenic hyperinsulinemia and hypoglycemia.

REMD-477 Background

Pharmacology

REMD-477 is a fully human IgG2 monoclonal antibody that binds to the human GCGR and antagonizes the effects of glucagon. In cell-based functional assays using recombinantly expressed glucagon receptors from various species, including human, mouse, rat, and cynomolgus monkey, REMD-477 blocks glucagon-induced cellular response (as measured by changes in cyclic AMP [cAMP] levels).

Both acute and chronic in vivo studies have been conducted with GCGR antibodies in normal mice, insulin-resistant diet-induced obesity (DIO) mice, and leptin-deficient *ob/ob* mice. Administration of GCGR antibodies lowered blood glucose in a dose-dependent fashion without inducing hypoglycemia in normal, DIO, and *ob/ob* mice. In a study conducted in normal cynomolgus monkeys, a single SC injection of the REMD-477 analog, 2-59.1, resulted in improved glucose tolerance as well as increased glucagon and GLP-1 levels. In the streptozotocin-induced T1DM model in mice, REMD2.59C (an REMD-477 analog) treatment totally corrected severe hyperglycemia (~500 mg/dL) after just the first weekly dose, normalized the HbA1c level to < 5%, and increased insulin immunostaining area in the islets, after 12 weekly doses of REMD-477 (Pharmaron, 2014). In another T1DM model induced by alloxan-injection in mice, an analog of REMD-477 (mAb Ac) corrected hyperglycemia after the 1st weekly injection, and normalized phosphorylated cAMP response element binding protein (p-CREB), a transducer of the glucagon signal, and suppressed phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme in gluconeogenesis (Wang, 2015).

In chronic rodent studies, the chimeric murine GCGR neutralizing antibody GR15c was used as a surrogate to assess the effects of blocking the glucagon pathway on hyperglucagonemia, alpha cell hyperplasia, and beta cell function. GR15c treatment caused dose-dependent hyperglucagonemia and minimal to mild alpha cell hyperplasia due to adaptive compensation for the reduced GCGR signal. There was no evidence in these studies of pancreatic alpha cell neoplastic transformation in mice treated with GR15c for as long as 18 weeks. Both treatment-induced hyperglucagonemia and alpha cell hyperplasia were reversible after treatment withdrawal for periods of 6 and 10 weeks. Importantly, pancreatic beta cell function was preserved, as demonstrated by improved glucose tolerance throughout the 18-week treatment period.

Preclinical Studies

Preclinical Pharmacokinetics

The PK of REMD-477 exhibited dose-dependent nonlinearity in mice, rats, and monkeys, as demonstrated by the decrease in clearance values and the more than dose- proportional increases in exposure (as assessed by C_{max} and AUC_{0-t}) with increasing doses over the 1- to 10-mg/kg dose range in mice and rats and over the 0.1- to 1-mg/kg dose range in monkeys. Limited extravascular distribution of REMD-477 was observed across species.

Upon multiple dosing of REMD-477, no marked accumulation was observed in monkeys following weekly subcutaneous (SC) dosing for 2 weeks, 4 weeks and 12 weeks, while minimal to moderate accumulation was observed by the 4th dose and 12th dose in rats following weekly SC dosing for 4 and 12 weeks, respectively.

The detection of anti-REMD-477 antibodies was associated with lower serum REMD-477 exposure in most of the animals from both PK and toxicology studies that developed antibodies.

Preclinical Toxicology

A comprehensive program of toxicology studies with REMD-477 has been conducted to support the clinical development of REMD-477. REMD-477 is pharmacologically active in rats and monkeys, making both appropriate species for nonclinical safety assessment of this monoclonal antibody. The program consisted of 2-week exploratory subcutaneous toxicity studies in rats, rabbits and monkeys (3, 30, and 300 mg/kg/dose for both studies), a 1-month subcutaneous toxicity study in rats (1, 30, 300 mg/kg/dose), a 1-month subcutaneous and intravenous toxicity study in monkeys, (3, 30, 300 mg/kg/dose), 3- month subcutaneous toxicity studies in rats (3, 30, and 300 mg/kg/dose) and monkeys (30, 100, and 300 mg/kg/dose), and a tissue cross-reactivity study. The 2-week study in rats and the 1-month studies included recovery periods of 6 weeks and 3 months, respectively, and the 3-month studies included 6-month recovery periods. Effects after a single dose of REMD-477 were assessed in neurobehavioral and respiratory safety pharmacology studies in rats, and local tolerance was assessed in the repeated-dose studies in rats and monkeys.

The acute toxicity potential of REMD-477, as assessed in safety pharmacology studies in male rats, appears to be low. The only effects observed on toxicity parameters after a single dose were decreases in body weight gain and food consumption that are considered to be mechanism-based effects of REMD-477, i.e., secondary to increases in plasma GLP-1. The effects on body weight and food consumption were not considered adverse. Furthermore, there are no adverse effects on neurobehavioral or respiratory parameters. Therefore, the NOAEL in these single dose studies was 300 mg/kg.

REMD-477 caused mechanism-based changes in subcutaneous toxicity studies in rats of up to 3-months in duration. Treatment-related changes included decreases in body weight gain and food consumption, increases in plasma glucagon and GLP-1, and hyperplasia of

pancreatic islet alpha cells. The 3-month recovery period following the 3-month treatment study in rats demonstrated full to partial reversal of all effects. None of the treatment-related changes were considered adverse. The NOAEL in rats after 3-months of weekly subcutaneous injections was 300 mg/kg/dose, the highest dose tested.

REMD-477 was also well tolerated in toxicity studies in monkeys in toxicity studies of up to 3-months in duration. As in the rat, all of the changes were considered secondary to blockade of the glucagon receptor. Decreases in food consumption and body weight were observed at the highest dose level tested (300 mg/kg). Increases in plasma GLP-1 were observed in monkeys, but a clear effect on plasma glucagon was not demonstrated. Treatment-related changes in the pancreas consisted of hypertrophy of pancreatic islet cells and decreased glucagon-immunolabeling. All of the changes observed in the 1- month study reversed completely during the 3-month recovery period. The NOAEL in monkeys after 3-months of subcutaneous injections was 300 mg/kg/dose, the highest dose tested.

Serum glucose levels were not meaningfully altered by treatment of rats or monkeys with REMD-477. A marked increase in plasma glucagon was observed in rats but not monkeys. Neither plasma insulin nor pancreatic insulin immunolabeling were altered by REMD-477 in either rats or monkeys.

Pancreatic alpha cell hyperplasia is an expected consequence of blockade of the glucagon receptor in rodents, and, as expected, REMD-477 caused alpha cell hyperplasia in toxicity studies in rats. Full to partial reversal of the alpha cell hyperplasia was demonstrated in rodent pharmacology and toxicology studies. In monkeys, hypertrophy, but not hyperplasia, of islet cells was observed and was also reversible.

REMD-477 caused minor inflammatory reactions at the subcutaneous injection site in some of the rat and monkey studies.

REMD-477 was immunogenic in both rats and monkeys. Some of the anti-REMD-477 antibodies decreased systemic exposure to REMD-477 and/or neutralized its activity. The development of these antibodies did not confound the interpretation of the toxicity studies since sufficient numbers of animals did not develop anti-REMD-477 antibodies, and, of those that did, a proportion developed changes characteristic of treatment with REMD-477. The development of anti-REMD-477 antibodies in animals is not necessarily relevant to the clinical use of REMD-477, since animal models cannot be solely used to predict the immunogenicity of fully human proteins in humans. Furthermore, since REMD-477 is not an

endogenous protein, the potential safety issues associated with neutralizing an endogenous protein's activity are diminished for this molecule.

Results of a tissue cross-reactivity study showed that binding of REMD-477 to normal tissues was similar between humans, cynomolgus monkeys, and Sprague-Dawley rats.

In summary, results of the nonclinical safety program for REMD-477 has defined a favorable safety profile for the molecule. In safety pharmacology studies in rats, REMD-477 did not cause adverse neurobehavioral or respiratory effects. There were no treatment-related cardiovascular effects in the toxicity studies in monkeys. No adverse effects were observed in toxicity studies of up to 12 weeks in duration in rats and monkeys that were conducted at doses up to 300 mg/kg. All treatment-related changes in these studies, except for minor inflammation at subcutaneous injection sites, were considered secondary to glucagon receptor blockade. Significant safety margins to proposed clinical doses exist. The nonclinical safety data for REMD-477 support clinical trials in humans of up to 12 weeks in duration.

Clinical Studies

FIH Study 20060310

In the first-in-human (FIH) study (Amgen Study 20060310) in healthy volunteers, 56 healthy adult subjects were planned to receive a single dose of placebo or REMD-477 at the following doses: 0.3, 1, 2.5, 5, and 10 mg/kg SC or 0.3 and 5 mg/kg IV. Forty (40) subjects (30 active: 10 placebo) received a single 0.3, 1, and 2.5 mg/kg SC dose, or a single 0.3 mg/kg IV dose of REMD-477. 38 subjects completed the study, but 2 subjects withdrew consent; one subject failed to return to follow up visits as instructed and another subject voluntarily withdrew consent.

A total of 30 normal volunteers received a single dose of REMD-477 at 0.3, 1 or 2.5 mg/kg SC, or 0.3 mg/kg IV. There appears to be no significant drug related adverse events. No deaths, dose limiting toxicities or withdrawals due to adverse events have been reported. No notable changes in ECG, safety lab tests (aside from the elevated AST/ALT noted below) or vital signs were reported. No hypoglycemia was observed across all dose cohorts.

All subjects in the FIH trial tested negative for the development of anti-REMD-477 antibodies.

Overall in this study, adverse events were reported for 17 of the 30 subjects (57%) who

received AMG477, and for 5 of the 10 subjects (50%) who received placebo.

Adverse events reported for more than 2 subjects were muscle strain for 3 subjects (REMD-477, 3/30 = 10%); and pharyngolaryngeal pain for 3 subjects (REMD-477, 2/30 = 7%; placebo, 1/10 = 10%). All adverse events were reported as mild or moderate in severity, with the exception of an event of ingrowing nail for a subject in the AMG 477 0.3-mg/kg IV group that was reported as severe. Adverse events were reported as treatment related for 6 of the 30 subjects (20%) who received REMD-477 at any dose, and for 1 of the 10 subjects (10%) who received placebo. Adverse events reported as treatment related for two or more subjects were increased alanine aminotransferase (ALT) for 2 subjects (REMD-477, 2/30 = 7%); asthenia for 2 subjects (REMD-477, 1/30 = 3%; placebo, 1/10 = 10%); and dizziness for 2 subjects (REMD-477, 2/30 = 7%). All adverse events reported as treatment related were also reported as mild or moderate in severity.

One serious adverse event of suicidal gesture was reported in a single subject 4 weeks after a single dose of 2.5 mg/kg REMD-477 SC. The subject ingested Tylenol-R, ibuprofen, and antibiotics; and was hospitalized. Treatment included catheterization, administration of charcoal, and a mental health evaluation. The event was considered moderate in severity, not related to study drug, and was resolved on the same day, and the subject was discharged from the hospital.

Elevations in aminotransferases (ALT and AST) without significant changes in bilirubin and/or alkaline phosphatase were observed and appeared to be dose dependent. Eight subjects in the REMD-477 SC groups (2 subjects in the 1 mg/kg group and 6 subjects in the 2.5 mg/kg group) experienced increases in ALT and/or AST to levels above the upper limit of normal (ULN) but ≤ 2.4 x ULN. Four subjects in the REMD-477 0.3 mg/kg IV group experienced increases in ALT and/or AST to levels above the ULN but ≤ 3.8 x ULN (peak ALT = 226 U/L; peak AST = 147 U/L). These ALT/AST increases occurred around 1-3 weeks after injection and were reversible afterwards. As the first study was designed to study the single dose, the effects of repeated dosing on AST/ALT changes need to be explored.

Compared with fasting glucose levels for subjects in the placebo group, levels for subjects in the REMD-477 groups appeared to decline after dosing and then gradually return toward baseline levels. The magnitude of the declines appeared to be dose-dependent. For instance, on day 4, mean fasting glucose levels were approximately 9%, 12%, and 13%

lower for the 0.3-mg/kg SC, 1-mg/kg SC, and 2.5-mg/kg SC REMD-477 dose groups, respectively, than for the placebo group. The glucose-lowering effects lasted 2 to 4 weeks, depending on the dose, with the maximum effects (~15%) occurring between Day 2 and 4.

FIH Study 20060310 – Clinical Pharmacokinetics

Following single SC administration of REMD-477 in healthy subjects, REMD-477 was slowly absorbed, with C_{max} observed at median T_{max} of 4 to 5 days post-dose. Exposure, as assessed by C_{max} and $AUC_{0\text{-}inf}$, increased more than dose-proportionally between the 0.3- and 2.5 mg/kg dose range. The effective half-life was approximately 2 weeks across dose groups. Mean residence time ($MRT_{0\text{-}t}$) increased with increasing dose and reached 317±63 hours at 2.5 mg/kg SC. Following IV administration of REMD-477 at 0.3 mg/kg, the C_{max} was between the C_{max} values from the 1 and 2.5 mg/kg SC cohorts. Exposure based on AUC for the 0.3 mg/kg SC dose group was approximately 25% of that achieved for the corresponding IV dose group.

Phase-1 Study T1DM: R477-101

Protocol R477-101 is a randomized, placebo-controlled, double-blind study to evaluate safety, tolerability and pharmacodynamics of REMD-477 in subjects who have Type 1 diabetes and are currently receiving insulin treatment. This proof of concept study evaluated whether glucagon receptor blockade using a single dose 70 mg SC of REMD-477 could decrease insulin requirements and improve glucose homeostasis versus placebo in patients with Type 1 diabetes. The study was completed in January, 2017.

Patients were admitted to an inpatient facility and evaluated over the course of 5 days. Insulin requirements to achieve tight glycemic control was determined on Day 1. On Day 2, insulin infusions were reduced to increase glucose levels to 250-300 mg/dL and REMD-477 or placebo was injected. On Days 3 and 4, insulin was then adjusted to maintain glycemic control similar to that achieved on Day 1. Continuous glucose monitoring was conducted throughout the study to evaluate glucose fluctuation, average glucose concentration, and percentage of time in range (70-180 mg/dL), percentage of time with low glucose concentrations (<70 mg/dL), and percentage of time with high glucose concentrations (>180 mg/dL).

A total of 21 patients were enrolled. Based on preliminary review of safety data review in January 2017, a single dose of 70 mg SC REMD-477 was safe and well-tolerated. There were

no significant drug related adverse events. No deaths, dose limiting toxicities or withdrawals due to adverse events have been reported. No notable changes in ECG, safety lab tests, or vital signs were reported. One patient whose treatment assignment remains blinded experienced an increase in ALT that was less than 1.6 times the upper limit of the laboratory normal on Days 22 and 50 after a single SC injection. There was no corresponding increase in bilirubin or alkaline phosphatase. The elevation occurred 21 and 49 days after administration of treatment which is not consistent with previous observations for liver enzyme increases in both healthy subjects and Type 2 diabetics which usually occur between 4-14 days after drug administration. No severe hypoglycemia was reported in the study patients.

An interim analysis of the first 17 subjects found REMD-477 treatment reduced daily insulin use by 32% (4.2%, 60%) vs. placebo on Day 4 (p=0.027). Average daily glucose assessed by CGM was 19 mg/dL (6.2, 31; p=0.006), and 26 mg/dL (8.2, 45; p=0.008) lower in the REMD-477 group than in the placebo group at Weeks 2 and 3 after treatment, respectively. Glucose time-in-range (70-180 mg/dL) for REMD-477 was 9.5% (2.7%, 16%; p=0.009) and 13% (1.9%, 25%; 0=0.026) greater in the REMD-477 group than in the placebo group during Weeks 2 and 3 after treatment, respectively.

Phase-1b-2a Study T2DM: R477-201

Protocol R477-201 is a randomized, placebo-controlled, double-blind, dose escalation study to evaluate safety, tolerability, PK and PD of single and repeated SC doses of REMD-477 in Type 2 diabetic subjects. The ongoing study includes a dose escalation phase (Part A) followed by an adaptive dose cohort phase (Part B) and two additional cohorts testing REMD-477 in combination with metformin (Part C).

In Parts A and B, approximately 72 subjects will be enrolled with Type 2 diabetes who are either treatment-naïve, controlled with diet and exercise or treated with oral antidiabetic medications. As of February 2017, 60 of subjects have been enrolled across 5 dose cohorts at dose levels of 14 mg, 28 mg, 35 mg, 42 mg, and 70 mg. Each cohort included 9 patients treated with REMD-477 and 3 treated with placebo. Patient received a single SC injection and 28 day observation followed by 8 weekly SC injections.

Part C of this study will enroll approximately 30 subjects with Type 2 diabetes who are currently on stable doses of metformin for at least 8 weeks. Each cohort will include 10 patients treated with REMD-477 and 5 treated with placebo. Patients will receive 12 weekly SC injections.

As of March 2017, the safety and tolerability of REMD-477 (multiple doses up to 70 mg SC) is available in 48 patients with T2DM. There are no significant drug related adverse events. No deaths, dose limiting toxicities or withdrawals due to adverse events have been reported. No notable changes in ECG or vital signs were reported. Importantly, there was no evidence of increased blood pressure. Mild reversible elevations of ALT up to 2.5x ULN were observed in 2 of 12 patients in the 42 mg cohort. At 70 mg, ALT increases up to 3x ULN were observed in 7 of 12 patients in the 70 mg cohort with a single isolated elevation of 18x ULN in one patient at one time-point that decreased below the ULN with continued dosing. Transaminase elevations were not associated with bilirubin or alkaline phosphatase increases. There were no other notable safety lab abnormalities observed. No hypoglycemia was observed across all dose cohorts.

Based on preliminary analysis, fasting glucose decreased 45-52 mg/dL relative to baseline after multiple doses of 14 mg to 42 mg while placebo treatment was associated with a decrease up to 10 mg/dL. Glucose AUC also decreased 130-172 h*mg/dL relative to baseline in the REMD-477 group versus placebo which showed decreases up to 39 h*mg/dL. HbA1c was evaluated at Days 57, 85, and 141 and showed a maximum decrease of 0.28%, 0.58%, and 1% for 14, 28, and 42 mg groups, respectively versus an increase of 0.03% for the placebo group.

Phase-1 b-2a Study T2DM: REMD-477-201 – Clinical Pharmacokinetics

Detailed plasma concentration over time profiles for REMD-477 were obtained at dose levels between 14 mg and 70 mg after the first and last SC injection. Consistent with results in healthy subjects (FIH Study 20060310), exposure, as assessed by C_{max} and $AUC_{0\text{-}inf}$, increased more than dose-proportionally between the 14 mg and 70 mg dose range. The effective half-life after single and multiple dosing was approximately 1 week across dose groups. Geometric mean accumulation ratio values were 11.2, 29.8, and 12.7 at the 14-, 28-, and 42-mg dose levels, respectively, indicating significant accumulation of REMD-477 after multiple dosing.

Dose Selection Rationale

The proposed dose design for the current study is for subjects to be randomized in a 1:1:1 fashion into one of three treatment groups (placebo, 35 mg REMD-477, or 70 mg REMD-477). 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. In

the subjects with Type 2 diabetes, increasing dose and exposure from 14 mg to 42 mg was associated with reduction in HbA1c. Based on available unblinded interim data, the maximum HbA1c reduction of 1% was achieved at 42 mg after 8 repeated weekly doses. In a blinded evaluation of the 70 mg cohort safety data, ALT increases were observed in a greater number of subjects relative to previous lower dose cohorts. In contrast, a single SC dose of 70 mg REMD-477 was not associated with significant increases in ALT in subjects with Type 1 diabetes. Only one subject who received blinded treatment had elevated ALT that were up to 1.6x ULN.

After a single dose of 70 mg of REMD-477 in subjects with Type 1 diabetes, significant reductions in insulin, average glucose, and time in range after CGM were observed. With repeated weekly dosing, substantial (10-30x) accumulation of REMD-477 is expected.

Based on the above findings, dose levels of 35 mg and 70 mg administered once weekly by SC injection over 12 weeks are being proposed. At these dose levels, significant improvements in glycemic control and reduction in insulin requirements are expected after multiple dosing. In addition, minimal to no transaminase elevations are expected based on the findings in Type 1 diabetics after a single 70 mg dose and the manageable transaminase elevations in Type 2 diabetics.

Hypothesis

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

3. EXPERIMENTAL PLAN

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 improve HbA1c after 12 weeks of treatment in subjects diagnosed with Type 1 diabetes and 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 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 arginine challenge will be examined. For subjects in Part A, alpha cell function will be assessed by measuring fasting glucagon, active and total glucagon-like peptide 1 (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 Baseline Overnight Visit (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 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.

Number of Centers

This study will be conducted at multiple (approximately 7 - 8) research centers in North America.

Number of Subjects

Approximately 150 subjects (75 in Part A and 75 in Part 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). Subjects will be enrolled in only one treatment group of the study.

Replacement subjects may be enrolled as per the Principal Investigator or REMD Biotherapeutics' discretion.

The sample size justification for subjects enrolled in this study is provided in Section 10 – Statistical Consideration.

Estimated Study Duration

Study Duration for Participants

Including the 42-day screening period, Lead-in Period of up to 4 weeks, study drug treatment period of 84 days and a safety follow-up period of 84 days, the maximum subject participation time is approximately 232 days.

End of Study

End of study is defined as having completed study procedures up to and including Day 162. Subjects who withdraw from study participation prior to the EOS visit date should complete EOS assessments and the early termination date will be the date of the final clinical evaluation.

4. SUBJECT ELIGIBILITY

Investigators will maintain a screening log of all potential study candidates that includes limited information about the potential candidate (age, sex, race), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or refused to participate).

Inclusion Criteria:

1. Men and women between the ages of 18 and 65 years old, inclusive, at the time of screening;
2. Females of non-child bearing potential must be ≥ 1 year post-menopausal (confirmed by a serum follicle-stimulating hormone (FSH) levels ≥ 40 IU/mL) or documented as being surgically sterile. Females of child bearing potential must agree to use two methods of contraception during the entire study and for an additional 3 months after the end of dosing with the investigational product;
3. Male subjects must be willing to use clinically acceptable method of contraception during the entire study and for an additional 6 months after the end of the treatment period;
4. Body mass index between 18.5 and 32 kg/m^2, inclusive, at screening (note that the subject's total daily insulin should be $\leq$ 1.0 unit/kg);
5. Diagnosed with Type 1 diabetes based on clinical history or as defined by the current American Diabetes Association (ADA) criteria;
6. HbA1c > 7% and < 10% at screening;
7. Fasting C-peptide < 0.7 ng/mL;
8. Treatment with a stable insulin regimen for at least 8 weeks before screening with multiple daily insulin (MDI) injections or continue subcutaneous insulin infusion (CSII)
9. Willing to use study-dedicated Continuous Glucose Monitoring (CGM) system (e.g. DexCom) throughout the study, subjects may continue to use personal CGM systems during the study but must be on stable use for at least 3 months prior to Screening;
10. ALT and/or AST ≤ 1.5x ULN at screening;

11. Able to provide written informed consent approved by an Institutional Review Board (IRB).

Exclusion Criteria:

1. History or evidence of clinically-significant disorder or condition that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion;
2. Significant organ system dysfunction (e.g., clinically significant pulmonary or cardiovascular disease, anemia [Hemoglobin < 10.0 g/dL], known hemoglobinopathies, and renal dysfunction [eGFR < 60 ml/min]);
3. Any severe symptomatic hypoglycemic event associated with a seizure or requiring help from other people or medical facility in the past 6 months;
4. Myocardial infarction, unstable angina, revascularization procedure, or cerebrovascular accident ≤ 12 weeks before screening;
5. History of New York Heart Association Functional Classification III-IV cardiac disease;
6. Current or recent (within 1 month of screening) use of diabetes medications other than insulin – subjects on an SGLT2 inhibitor should discontinue the SGLT2 inhibitor during the Screening Period, at least 2 weeks prior to the start of the Lead-in Period;
7. Use of steroids and/or other prescribed or over-the-counter medications that are known to affect the outcome measures in this study or known to influence glucose metabolism;
8. Smokes > 10 cigarettes/day and/or is unwilling to abstain from smoking during the admission periods;
9. Known sensitivity to mammalian-derived drug preparations, recombinant protein-based drugs or to humanized or human antibodies;
10. History of illicit drug use or alcohol abuse within the last 6 months or a positive drug urine test result at screening;
11. History of pancreatitis, pancreatic neuroendocrine tumors or multiple endocrine

neoplasia (MEN) or family history of MEN;

12. History of pheochromocytoma, or family history of familial pheochromocytoma;
13. Known or suspected susceptibility to infectious disease (e.g. taking immunosuppressive agents or has a documented inherited or acquired immunodeficiency);
14. Known history of positive for human immunodeficiency virus (HIV) antibodies, hepatitis B surface antigen (HbsAg), or hepatitis C antibodies (HepC Ab);
15. Participation in an investigational drug or device trial within 30 days of screening or within 5 times the half-life of the investigational agent in the other clinical study, if known, whichever period is longer;
16. Blood donor or blood loss > 500 mL within 30 days of Day 1;
17. Women who are pregnant or lactating/breastfeeding;
18. Unable or unwilling to follow the study protocol or who are non-compliant with screening appointments or study visits;
19. Any other condition(s) that might reduce the chance of obtaining study data, or that might cause safety concerns, or that might compromise the ability to give truly informed consent.

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, REMD Biotherapeutics, Inc. requires a copy of the site's written IRB approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable. A subject is considered enrolled once the subject is randomized. However, if a subject has been randomized and does not receive study drug, the subject may be replaced. All subjects must personally sign and date the informed consent form, before any study specific procedures are performed.

All subjects who enter into the screening period for the study (defined as the point at which the subject signs the informed consent) will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening, enrollment, or randomization. This number will not be the same as the randomization number assigned for the study. Screening procedures/tests may be repeated and reevaluated per Investigator discretion and sponsor approval.

The unique study identification number will consist of 7 digits. The first 3 digits will represent the last 3 digits of the protocol number (e.g., 202). The 4th digit will be an alphabet representing the site code (i.e., site number for the first center is A, site number for the second center is B) and will be identical for all subjects at the same site. The next 3 digits will be assigned in sequential order as subjects are screened (e.g., 001, 002, 003). For example, the first subject to enter screening at site A will receive the number 202A001, and the second subject at the same site will be 202A002.

Treatment Assignment

Subject eligibility will be established at the conclusion of the baseline evaluations, and subjects will then be randomized in a double-blind fashion. The proposed dose design for the current study is for subjects to be randomized in a 1:1:1 fashion into one of three treatment groups (placebo, 35 mg REMD-477, or 70 mg REMD-477).

Enrollment will take place at 7 to 8 centers in North America. A blinded central randomizer identified by REMD Biotherapeutics will be used to assign the randomization number for all subjects randomized into this study. The unblinded pharmacist or designee at each of the

sites will prepare study drug according to the randomization schedule.

Randomization

Randomization to placebo, 35 mg REMD-477, or 70 mg REMD-477 will be based on a randomization schedule prepared by the CRO's designated unblinded biostatistician and provided to each of the unblinded site pharmacist or designee before the start of the study.

Subjects will be considered randomized once a unique subject randomization number has been assigned. Randomization of a subject may occur within a day prior to Day 1, after subject's eligibility has been confirmed.

After subjects have completed the screening procedures and are confirmed to be eligible for the study, they will be assigned a 5-digit randomization number based in the sequential order in which they met eligibility. The 5-digit randomization number will follow the convention SRXXX, where S is the site code (A, B, C, D, E, F, G, or H), R is a replacement number (with the initial subject to be marked as "0"), and XXX is a sequential randomization number from 001 to 075 for Part A of the Protocol, and 101 to 175 for Part B of the Protocol.

In the event subjects are randomized, but are withdrawn before receiving study medication, a replacement subject may be enrolled in the subject's place and assigned to receive the identical treatment as the replaced subject. The replacement subject will receive a randomization number that is identical to the replaced subject, except that the number '1' will be added to replace "0" in the thousands place of the 5-digit randomization number (e.g., subject A1001 replaces subject A0001).

6. TREATMENT PROCEDURES

Investigational Product Dosage, Administration, and Schedule

REMD-477 will be manufactured and packaged by a certified contract manufacturing organization (CMO) and distributed using GCP-compliant clinical trial drug distribution procedures. REMD-477 is supplied as single-use glass vials. REMD-477 is formulated with 10mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20 at a protein concentration of 70 mg/mL.

The formulation of placebo is 10 mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20. REMD-477 or vehicle is to be administered SC using 1 mL size insulin syringes.

Approximately 150 subjects (75 in Part A and 75 in Part B) 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).

SC doses of placebo, 35 mg REMD-477, or 70 mg REMD-477 will be administered at the CRU by a qualified staff member on Day 1, followed with repeated weekly doses for an additional 11 weeks. Twelve total weekly SC doses of placebo, 35 mg REMD-477, or 70 mg REMD-477 will be administered at the CRU by a qualified staff member on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Each subject will receive his/her study drug SC injections at the same time of the day as administered on Day 1 (+/- 1 hour).

Each dose will be divided into two blinded 0.5 mL volume SC injections administered to the subject's anterior abdominal wall, for a total dose volume of 1 mL. For the 70 mg REMD-477 dose group, subjects will receive two 0.5 mL SC injections of 70 mg/mL REMD-477 on each scheduled day of dosing. For the 35 mg REMD-477 dose group, subjects will receive one 0.5 mL SC injection of 70 mg/mL REMD-477 and one 0.5 mL SC injection of placebo on each scheduled day of dosing. For the placebo dose group, subjects will receive two 0.5 mL SC injections of placebo on each scheduled day of dosing. For each scheduled dose, the two 0.5 mL SC injections should be placed at a distance of 2 cm apart. Alternating (left or right) sites on the subject's anterior abdominal wall and at a distance of at least 2 cm apart will be used for subsequent SC dosing.

The Principal Investigator or a designee must be present during administration. Documentation of the investigational product or matching placebo administration will be

noted on the electronic case report form (eCRF) page and in the source documents. The date, dosage and time of administration for dose will be recorded on the respective eCRF page.

The effects of overdose of REMD-477 are not known. All overdose occurrences must be documented, and corresponding AEs recorded on the appropriate eCRF page and in source documents.

The Pharmacy Guide is provided in Appendix B. Details in preparing and administering all study products are included in the Pharmacy Binder provided by REMD Biotherapeutics prior to the start of the study.

Other Protocol-Required Drugs

There are no other protocol-required drugs.

Safety Data Review and Stopping Rules

Safety Review Committee

The Safety Review Committee meeting will be held via teleconference to review available study data and monitor subject safety. The Safety Review Committee will be composed of the Investigator(s) and REMD Biotherapeutics Medical Monitor and Clinical Operations Director. Additional members may be added as needed. The Committee may recommend to continue dosing, to delay dosing, to increase enrollment, to disqualify a subject, or to decrease/increase dose based on emerging safety, PK, and PD data from this current study or the completed phase 1b/2a study (Protocol R477-201) in type 2 diabetic subjects. Final decisions will be determined by the ~9 -12 voting Safety Review Committee members who include the REMD Biotherapeutics medical monitor and clinical operations director, and the 7- 8 Investigators. At least three fourths of the voting Safety Review Committee members must agree to the decision. All available study data including demographics, medical history, concomitant medications, adverse events, ECG, vital signs, and laboratory results will be reviewed. Data to be reviewed may not necessarily be validated and cleaned (data query resolution may be pending).

Data will be reviewed blinded (i.e., treatment assignment will not be revealed) unless unblinding is deemed necessary for the Safety Review Committee. If deemed necessary, unblinding will be performed according to REMD Biotherapeutics standard procedures.

Safety Data Review

Study recruitment, progress and safety issues will be reviewed by the investigators, research nurse and research coordinators and communicated to the sponsor on a regular basis. The following will be reviewed: 1) subject enrollment, 2) preliminary findings that might affect the risk/benefit ratio or alter the procedures described in the protocol, 3) any clinically-significant out-of-range laboratory value and a course of action, and 4) any adverse or serious adverse events that might result from the research procedures.

The Safety Review Committee will review all available safety and PD data periodically during the study when approximately 33%, 66%, and 100% of the subjects in Part A have received a randomized treatment. After each safety data review, the Safety Review Committee will decide whether or not to continue with subject enrollment and dosing. Decisions to continue enrollment will be documented in the Safety Review Memo. REMD Biotherapeutics will issue a written notification of these decisions to investigators.

Determination of Adverse Event Severity and Relatedness

Adverse events will be coded per current MedDRA. Determination of the severity of adverse events will be consistent with Common Terminology Criteria for Adverse Events (CTCAE) V. 4.03. The relationship of an adverse event to treatment will be determined by the Investigator (see section 9: Reporting Procedures for All Adverse Events).

Dose Stopping Rules

Dosing will be stopped or modified if treatment-related AEs, changes in vital signs, ECG, or clinical laboratory results are observed and these changes pose a significant health risk, in the opinion of the Sponsor, Principal Investigator or Medical Monitor.

Medically significant AEs considered to be related to the investigational product and serious adverse events considered to be related to study procedures will be followed until resolved or considered stable.

A subject may be terminated at any point in time at the discretion of the Sponsor, Principal Investigator or Medical Monitor.

Stopping Rules for an Individual Subject:

At any time during the study, the subject must discontinue study drug treatment, if one of the following events occur:

- An increase of AST and/or ALT (> 3x ULN) are observed in the presence of increased (> 2x ULN) alkaline phosphatase and/or total bilirubin.
- A sustained AST or ALT increase, defined as three consecutive values of AST and/or ALT greater than 5x ULN within a period of 14 days.
- A treatment-related Grade 3 or greater adverse event (other than AST or ALT increase as described above) is noted by the Investigator.

If any of the above stopping rules are met the following action(s) should be taken:

1. Stop dosing and convene a Safety Review Committee meeting;
2. Review AE for evidence of relationship to treatment;
3. Consider unblinding, as appropriate*;
4. May resume enrollment and continue the study if recommended by the Safety Review Committee.

**A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject, or may impact the safety of subjects currently enrolled.*

Concomitant Therapy

Throughout the study, the Principal Investigator may prescribe concomitant medications or treatments deemed necessary to provide adequate medical care.

For subjects enrolled in this study, the allowable concomitant medications include insulin, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta adrenergic receptor blockers, calcium channel blockers, diuretics, HMG-CoA reductase inhibitors, fibrates, low-dose aspirin, NSAIDs, and hormone replacement therapies (estrogen or thyroid). Subjects on an SGLT2 inhibitor should discontinue the SGLT2 inhibitor during the Screening period, at least 2 weeks prior to the start of the Lead-in Period. The use of any other concomitant medication requires Investigator's discretion and must not interfere with the study outcomes. Doses of allowable concomitant medications must be stable for > 1 month prior to Day 1.

Any use of concomitant therapy or treatments will be recorded in the applicable eCRF page with appropriate source documentation.

Proscribed Therapy during Study Period

Current or recent (within 1 month of screening) use of diabetes medications other than insulin, or use of other medications that are known to affect the outcome measures are prohibited for this study.

No other medication (with the exception of those listed above) is to be taken within 2 weeks or 5 half-lives (whichever time period is greater) before Day 1 and through the duration of the study. All herbal or nutritional supplements are subject to investigator's discretion.

Any concomitant medication used to treat a medical emergency or as rescue medication for hyperglycemia will be subject to investigator's review and endorsement for continuation in the study, and will be documented on the appropriate eCRF page and in the source documentation.

7. STUDY PROCEDURES

The study will include several parts: Screening Period, Lead-In Period, Baseline Visit, a 12 week treatment period, and a 12 week safety follow-up period. During the study, every effort should be made to perform the study procedures as indicated in the Schedule of Assessments (Appendix A).

All visits, tests, examinations or specimen collections that are not completed must be reported in the source documents and recorded on the appropriate eCRF page.

All post-dose time points are relative to the time of dosing. Time of dosing is designated as time = 0 hour. When multiple procedures are scheduled at the same time point, the ECG takes precedence over blood collection (i.e., PK sampling, safety testing).

Screening Visit:

All experimental procedures will be explained in writing and orally to the subject by the principal investigator, co-investigator, or appropriate research staff. The objectives of the project, all of the requirements for participation, and any possible discomforts and risks will be clearly explained to each subject orally and in writing in lay terms that he/she is able to comprehend. The subject must sign an IRB-approved informed consent form before participating in any aspect of the study. Subjects may be screened up to 42 days prior to initiating the Lead-in Period. If a subject falls outside the 42 day screening window and continues to remain eligible, the screening window may be extended, but the Screening procedures outside the 42 day screening window must be repeated.

A medical examination, including medical history and physical examination, hematology and blood chemistry, urine tests (including urine pregnancy tests for female subjects), a 12-lead ECG, and other screening tests will be performed as specified in the Schedule of Assessments.

Lead-In Period:

The Lead-in Period applies to all subjects and may begin when a subject is judged by an investigator to be eligible, after the initial screening. For subjects participating in Part A, the Lead-In Period may last between 2 and 4 weeks. For subjects participating in Part B, the Lead-in Period may last between 1 and 2 weeks. The subject will be given a DexCom CGM and subjects in Part A will be required to wear it for a minimum duration of two weeks prior to

the **Baseline Visit**, while subjects in Part B will be required to wear it for a minimum duration of 1 week prior to the **Day 1** Visit. Insulin treatment will continue, and the subject will be given an insulin usage diary. Assessments of daily insulin use (short-acting, long-acting, and infusional, as appropriate) will be recorded over a 14 day period prior to the Baseline Visit for subjects in Part A, or over a 7 day period prior to the Day 1 Visit for subjects in Part B. During the Lead-In Period, subjects will also record their blood glucose levels in a seven-point glucose profile over a single period of three consecutive days prior to the Baseline Visit (subjects in Part A) or the Day 1 visit (subjects in Part B).

Overnight Baseline Visit (OBV) - applies to a subset of subjects in Part A who were enrolled prior to Protocol Amendment #1**:**

After the Lead-in Period (which includes the completion of the two week CGM period), eligible subjects will be admitted to the CRU around 4:00 pm for a single overnight stay on one of the following study days: Day -8, -7, -6, -5, -4, -3, or -2 relative to the subject's scheduled dosing day (Day 1). The OBV must be performed within 2 to 8 days (check-in to occur between Day -8 to Day -2) prior to administration of study drug.

At the time of admission, data from the DexCom CGM device, the subject's diary capturing insulin use, and the seven-point glucose measurements will be obtained and reviewed. CGM results from the study DexCom device will be downloaded, and typical measures of glycemic control (mean glucose, standard deviation, time in range) will be recorded. CGM results will be unblinded throughout the study.

Additionally, the following baseline assessments will be completed: medical history, physical exam, body weight, urine pregnancy test, urine drug and alcohol test, 12-lead ECG, and vital signs, per the Schedule of Assessments. Safety and PD labs including serum chemistry, hematology, urinalysis, HbA1c, insulin, C-peptide, glucagon, serum ketones, free fatty acids, and GLP-1 will be collected. Fasting plasma glucose samples will be collected on the following morning, prior to the administration of the MMTT and Arginine Challenge Tests. During the 8 hour overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia.

For subjects on insulin pumps: Subjects will be admitted to the CRU at approximately 1600 (4:00 pm). A peripheral IV will be placed at this time. They will be given a standard dinner at 1800 (6:00 pm) for which they can bolus as they normally would via their insulin pump for that

particular meal. At approximately 1900 (7:00 pm), the subjects insulin pump will be disconnected and suspended and IV insulin infusion will begin. Blood glucose control will be maintained per Appendix C to maintain euglycemia in the 90-120 mg/dl range with start rates described in also in Appendix C. The MMTT and arginine challenge will then be performed the next morning at approximately 8:00 am [please note: the insulin infusion will continue until the completion of the both the MMTT and Arginine challenge Test assessments]. After completing the 2 hour MMTT, subjects will be administered an arginine challenge test. During both challenge tests, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia. Upon completion of all tests, subjects may be given additional insulin via SC injection or a bolus of insulin via either IV or insulin pump, at the discretion of the investigator. Additionally, the subject's insulin pump will be restarted immediately after completion of all tests. Subjects will be monitored closely by CGM and YSI as needed and discharged only after blood glucose is < 250mg/dl and relatively stable (not rapidly declining).

For subjects on insulin injections with basal insulin given at night: Subjects can take their last dose of long acting insulin 1 day prior to admission in the evening. They will be admitted and be administered SC or bolus insulin as they would with their rapid acting injection for dinner. Insulin infusion via IV will start at 7:00 pm. No basal insulin injection will be given SC on the night of admission. After all study procedures have been completed the next morning, subjects may receive additional insulin via SC injection or a bolus of insulin via IV, at the discretion of the investigator. At that time they should take half their normal dose of basal insulin SC. They can take the second half at their usual time later that evening. The following day, they can resume their full, normal basal insulin dose.

For subjects on insulin injections with basal insulin given in the morning: Subjects will take their normal AM dose of basal insulin on the morning of the day of admission. They will be admitted and be administered SC or bolus insulin as they would with their rapid acting injection for dinner. IV insulin will be started at 7:00 pm. Of note, given that subjects will have their basal insulin working overnight, they will likely require much less IV insulin, and thus per Appendix C will be started on a much lower infusion rate. After all study procedures have been completed the next morning, the subject may receive additional insulin either via SC injection or an IV bolus (at the discretion of the investigator), and subjects will take their regular dose of basal insulin. The following day they can resume their dose in the morning as they usually would.

Baseline Visit (BV) - applies to subjects in Part A who are enrolled at the time of Protocol Amendment #1:

After the Lead-in Period (which includes the completion of the two week CGM period), eligible subjects will return to the CRU after completing an 8 hour overnight fast at home on the morning of one of the following study days: Day -8, -7, -6, -5, -4, -3, -2 or -1 relative to the subject's scheduled dosing day (Day 1). For subjects who are enrolled at the time of this Protocol Amendment, overnight admission to the CRU will not occur.

At the beginning of the visit, data from the DexCom CGM device, the subject's diary capturing insulin use, and the seven-point glucose measurements will be obtained and reviewed. CGM results from the study DexCom device will be downloaded and typical measures of glycemic control (mean glucose, standard deviation, time in range) will be recorded. CGM results will be unblinded throughout the study.

Additionally, the following baseline assessments will be completed: medical history, physical exam, body weight, urine pregnancy test, urine drug and alcohol test, 12-lead ECG, and vital signs, per the Schedule of Assessments. Safety and PD labs, including serum chemistry, hematology, urinalysis, HbA1c, insulin, C-peptide, glucagon, serum ketones, free fatty acids (FFA), and GLP-1 will be collected. Fasting plasma glucose samples will also be collected, prior to the administration of the MMTT. For all subjects, fasting blood glucose should be 80-180 mg/dl. During the overnight fasting at home, subject can drink juice or take glucose tabs if hypoglycemic. No rapid acting insulin should be taken within 4 hours prior of the MMTT. During the MMTT, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia.

For subjects on insulin pumps: The insulin pump will continue until the completion of the MMTT.

For subjects on insulin injections with basal insulin given at night: Subjects can take their last dose of long acting insulin in the evening prior to the Baseline Visit.

For subjects on insulin injections with basal insulin given in the morning: Subjects will take their normal AM dose of basal insulin in the morning a day prior to the Baseline Visit, as well as on the morning of the MMTT.

Upon completion of all tests, subjects may be given additional insulin via SC injection or a bolus of insulin via either IV or insulin pump, at the discretion of the investigator. Subjects will be

monitored closely by CGM as needed and discharged only after blood glucose is < 250 mg/dl and relatively stable (not rapidly declining).

Please Note: Neither the Overnight Baseline Visit (OBV) nor the Baseline Visit (BV) apply to subjects enrolled in Part B.

Randomization and Day 1 Treatment for Subjects Enrolled in Part A: Week 1

On the morning of Day 1, eligible subjects will return to the CRU and will be randomized to placebo or REMD-477 at 35 mg or 70 mg, and undergo pre-dose safety, laboratory, and PD measurements as outlined in the Schedule of Assessments.

After completion of the pre-dose Day 1 tests and procedures, subjects will be administered study drug by SC injection. Upon completion of post-dose procedures, subjects will be discharged from the CRU when the Investigator feels that the subject's condition is stable.

Subjects will also be given the "Week 1" insulin usage diary to record daily insulin use. For Week 1, assessments of daily insulin use will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days. To mitigate a potential risk of hypoglycemia, subjects with HbA1C ≤ 8.0% at screening, at the discretion of the investigator, may reduce their total insulin dose by 10-20% on the day of randomization. Hypoglycemia of different magnitudes will be evaluated via CGM. For this study, the primary threshold for hypoglycemia will be set at ≤ 70 mg/dl and second threshold at <54 mg/dL.

Baseline, Randomization and Day 1 Treatment for Subjects Enrolled in Part B: Week 1

After the Lead-in Period (which includes the completion of the one week CGM collection period), eligible subjects will return to the CRU for the Day 1 Visit and will be randomized to placebo or REMD-477 at 35 mg or 70 mg. Prior to being dosed, the subject will undergo all pre-dose safety, laboratory, and PD measurements as outlined in the Schedule of Assessments, as these will serve as the subject's baseline.

After completion of the pre-dose Day 1 tests and procedures, subjects will be administered study drug by SC injection. Upon completion of post-dose procedures, subjects will be discharged from the CRU when the Investigator feels that the subject's condition is stable.

Subjects will also be given the "Week 1" insulin usage diary to record daily insulin use. For

Week 1, assessment of daily insulin use will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days (starting on Day 1). For this study, the primary threshold for hypoglycemia will be set at ≤ 70 mg/dl and second threshold at < 54 mg/dL.

For Dose 2 through Dose 12: Week 2 through Week 12

Subjects will return to the CRU on an outpatient basis to receive weekly SC injections of REMD-477 or placebo for a total of 12 injections. Follow-up phone calls by the research staff will occur 3-4 days after Dose 1 and Dose 2 to assess subject insulin use and glucose control and to coach the subject on insulin dosing as needed to minimize hypoglycemia. Safety, PK, and PD assessments will be conducted on an outpatient basis at various time points as described in the Schedule of Assessments. These assessments will include physical exam, body weight, urinary pregnancy test (women), urine drug and alcohol test, 12-lead ECG, vital signs, serum chemistry, hematology, urinalysis HbA1c, insulin, C-peptide, glucagon, GLP-1, and REMD-477 serum concentrations, and fasting glucose (subjects should be instructed to fast overnight for 8 hours prior to collection). For subjects enrolled in Part B, additional safety assessments will include blood collection for liver injury biomarkers at timepoints outlined in the Schedule of Assessments – Part B.

Subjects will be given an insulin usage diary at the beginning of Weeks 2 through 4 to record daily insulin use. For Weeks 2 through 4, assessments of the daily insulin requirements will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) collected over seven days.

Subjects will also be given an insulin usage diary at the beginning of Weeks 8 and 12. For these weeks, assessments of daily insulin use will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) over a period of three consecutive days within that respective week.

Follow-up and End of Study (EOS): Week 13 through Week 24

Subjects receiving all 12 doses will be followed for 12 weeks after the last dose and will complete study evaluations as described in the Schedule of Assessments.

At Week 13 (1 week after receiving Dose 12) and Week 24 (End of Study Visit), a subset of subjects in Part A enrolled prior to Protocol Amendment #1 will be admitted to the CRU to

complete an MMTT and arginine challenge test, after an overnight fast of at least 8 hours in a similar manner as done at the Overnight Baseline Visit. During the 8 hour overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia. During both challenge tests, C-peptide, glucagon, insulin, GLP-1, and glucose concentrations will be measured. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia.

For ongoing or newly enrolled subjects participating in Part A at the time of Protocol Amendment #1, overnight admissions to the CRU at Week 13 and Week 24 will not occur. For these visits, subjects will still return to the CRU to complete all the study procedures outlined in the Schedule of Assessments table – however, all assessments for that visit will be performed on a single day (i.e., the Week 13 Visit will be performed on Day 85, and the Week 24 Visit will be performed on Day 162).

For subjects enrolled in Part A:

- **Please Note:** For ongoing or newly enrolled subjects at the time of Protocol Amendment #1, the MMTT will only be administered at the Baseline and Week 13 visits, after the subject completes an 8 hour overnight fast at home (the MMTT is no longer required at Week 24). No Arginine Challenge Tests or YSI assessments will be performed for these subjects.

For subjects enrolled in Part B:

- **Please Note:** Neither the MMTT assessment nor Arginine Challenge Test assessment will be conducted.

Subjects will also be given an insulin usage diary at the beginning of weeks 16 and 20. For these weeks, assessments of the daily insulin requirements will be obtained by taking the average total daily insulin dose (short-acting, long-acting, and infusional as applicable) over a period of three consecutive days within that respective week.

Subjects who early terminate from the study during the 12-week treatment period will be monitored for 12 weeks after the last injection of study drug (REMD-477 or placebo).

Throughout the Study: Day 1 through End of Study

Subjects will be instructed to titrate their basal insulin dose to achieve a pre-breakfast blood glucose level of 4.4-6.6 mmol/L (80-120 mg/dL) and to titrate their bolus insulin dose to achieve a pre-lunch, pre-dinner, and bedtime blood glucose level of 4.4-6.6 mmol/L (80-120 mg/dL). Algorithms for titrating basal and bolus insulin doses to achieve target glycemic goals will be provided. Subjects' basal and bolus doses may also be adjusted at the discretion of the investigator's typical standard of care.

Adverse events and concomitant medications (including non-prescription medications and/or supplements such as protein / amino acid supplements) will be collected throughout the study when reported. Any rescue medications and use of meals/food to manage hypoglycemic sensations or events will be reviewed carefully with the subject and recorded accordingly. If there is a clinically significant laboratory abnormality or adverse event in need of monitoring, subjects will be followed until resolution of the abnormality or adverse event or until it is considered stable.

For subjects participating in Part A, CGM data will be collected throughout the study from Dose 1 through the End of Study Visit, and CGM devices will be "unblinded". For on-going or newly enrolled subjects in Part A at the time of Protocol Amendment #2, CGM data will be collected throughout the study from Dose 1 through the Day 85/Week 13 Visit, and CGM devices will be "unblinded". For subjects participating in Part B, CGM devices will be configured in a "blinded" fashion, wherein the CGM data will not be accessible to the subject or the Investigator, and will be collected for one week intervals during specified time periods noted in the Schedule of Assessments – Part B (study weeks 1, 4, 8, and 12, after receiving that week's assigned dose).

Seven-point blood glucose profiles (measuring glucose via finger stick, at the following times of day: before each meal, 2 hours after each meal, and at bedtime) will be performed for periods of three consecutive days. During the **Lead-In Period**, subjects will record their seven-point blood glucose (BG) profile over a period of three consecutive days either, prior to the Baseline Visit (subjects participating in Part A), or prior to the Day 1 Visit (subjects participating in Part B). During the **12 week Dosing Period** and **12 week Follow-up Period**, seven-point BG profiles will be performed over the three consecutive days following Dose 4 (Study Days 23 – 25), Dose 8 (Study Days 51 – 53), and Dose 12 (Study Days 79 – 81), and during Weeks 16 and 20 of the Follow-up Period.

Subjects will be provided with a blood ketone meter and blood ketone test strips in order to

measure blood ketone readings via finger-stick method. For subjects in Part A only, blood ketone readings will be performed in the morning and collected by the subject while in a fasted state, prior to the subject's morning meal. During the 12-Week Dosing Period (starting on Day 1 and continuing through the completion of Week 12) the blood ketone readings will be performed 3 days a week – on an alternate day basis starting on Day 1 (e.g. Week 1: Study Days 1, 3, 5 or on Mondays, Wednesday, and Fridays), and once weekly during the 12-Week Follow-up Period. Subjects will be instructed to contact the investigator if they have positive ketones and blood sugars > 300mg/dL. Subjects enrolled in Part B will also be provided with a blood ketone meter and blood ketone test strips to be used as needed, however, there is no required collection schedule. Subjects in Part B will be advised to perform blood ketone readings via finger-stick method when they feel ill, or symptomatic of ketoacidosis, or as instructed by the investigator.

The Type 1 – Diabetes Distress Scale (T1-DDS) and WHO-5 Well-Being Index scales (Appendix D) will be provided to the subject at the beginning of the following study visits: OBV and Day 85 and Day 161(EOS) visits.

PK blood samples and fasting plasma glucose samples will be collected as described in the Schedule of Assessments. For those samples that are scheduled for collection on days when study drug is administered, those samples should be collected pre-dose.

Anti-REMD-477 antibody samples will be collected pre-dose on Days 1, 85, and at the End of Study Visit (Day 162).

For a subset of subjects participating in Part B, a 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. Also, blood samples to measure biomarkers of liver injury will be collected from Part B subjects on Day 1 (pre-dose), Day 29 (Week 5) , Day 57 (Week 9), Day 85 (Week 13), and Day 106 (Week 16).

Medical History

A complete medical history will be obtained within 42 days of the Lead-in Period, and again during the OBV or at the Baseline Visit, prior to Day 1 by the Principal Investigator or designee. Medical history will include information on the subject's concurrent medical illness and

prescription & non-prescription medications (including supplements such as protein and/or amino acid supplements). The medical history findings will be recorded on the eCRF page with appropriate source documentation.

Physical Examination

The Principal Investigator or qualified designee will perform a physical examination at screening and time points outlined in the Schedule of Assessments (Appendix A). Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the baseline physical examination, which represents a clinically significant deterioration, will be documented on the adverse events page of the eCRF. All findings must also have appropriate source documentation.

Height measurement (in centimeters and without shoes) will be obtained at screening. Weight measurement (in kg and without shoes) will be obtained at Screening, OBV or Baseline Visit, and Days 29, 57, 84, 106, 134 and 162/EOS. Body Mass Index (BMI) will be calculated using height and weight measurements taken at the Screening Visit and OBV or Baseline Visit for subjects and using the following formula:

$$BMI = \frac{weight\ (kg)}{height\ (m)^2}$$

Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate and oral temperature, will be measured by the Principal Investigator or qualified designee at the time points listed in the Schedule of Assessments (Appendix A).

Subjects must be seated or in a semi-recumbent position for at least 5 minutes prior to vital signs measurement. All measurements will be recorded in the source documents and recorded on the appropriate eCRF page. Any abnormal measurements may be repeated and reported on the eCRF page with appropriate source documentation. When vital signs and blood sample collection occur at the same time, vital signs should be performed before blood samples are drawn.

Electrocardiogram

Twelve-lead ECGs reporting ventricular rate, PR, QRS, QT and QT_cF intervals will be obtained by the Principal Investigator or designee at the time points indicated in the

Schedule of Assessments (Appendix A). Subjects should be supine for at least 5 minutes before each ECG is obtained. A single ECG will be performed at screening.

At the Baseline Visit, ECGs will be performed (in triplicate approximately one minute apart) will be considered baseline ECGs. All other ECG collections will be single tracings. When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

The Principal Investigator or qualified designee will review all ECGs. The original ECG tracings will be maintained in the source documentation of each subject.

Adverse Events and Concomitant Medications

Subjects will be assessed for adverse events (Section 9) and concomitant medications (including non-prescription medications and/or supplements such as protein / amino acid supplements) at least daily during residency periods and during each outpatient visit as outlined in the Schedule of Assessments (Appendix A). Any rescue medications and use of meals/food to manage hypoglycemic sensations or events will be reviewed carefully with the subject and recorded accordingly. Any AEs or concomitant medication use reported throughout the study will be recorded in the eCRF with appropriate source documentation.

Continuous Glucose Monitoring (CGM) and Glucose Blood Monitoring

Subject's glucose levels will be monitored using the DexCom CGM device. The CGM device will be used to track blood sugar levels day and night, and it will collect readings automatically every 5 minutes. CGM uses a tiny sensor placed under the skin of the subject's belly and measure blood glucose levels.

During the Lead-in Period, the subject will be given a DexCom CGM and subjects in Part A will be required to wear it for a minimum duration of two weeks prior to the Baseline Visit, while subjects in Part B will be required to wear it for a minimum duration of one week prior to the Day 1 Visit. At either the Baseline Visit (Part A subjects) or the Day 1 visit (Part B subjects), data from the CGM device and record of insulin use will be obtained and reviewed (please note: CGM data will not be reviewable for Part B subjects). Data will be downloaded and typical measures of glycemic control (mean glucose, standard deviation, time in range) will be recorded (please note: downloaded CGM data will remain unreviewable for Part B subjects). Assessments of the pre-study daily insulin requirements will be obtained by

taking the average total daily insulin dose over a 14 day period prior to the Baseline Visit for subjects in Part A, or over a 7 day period prior to the Day 1 Visit for subjects in Part B.

For subjects enrolled in Part A, CGM data will be collected throughout the study from Dose 1 through the End of Study Visit, and CGM data will be "unblinded". For on-going or newly enrolled subjects in Part A at the time of Protocol Amendment #2, CGM data will be collected throughout the study from Dose 1 through the Day 85/Week 13 Visit, and CGM devices will be "unblinded". Although CGM will be conducted throughout the study from Dose 1 through the 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.

For subjects in Part B, CGM devices will be configured in a "blinded" fashion, wherein the CGM data will not be accessible to the subject or the Investigator, and will be collected for one week intervals, during specified time periods noted in the Schedule of Assessments – Part B (study weeks 1, 4, 8, and 12, after receiving that week's assigned dose).

Mixed Meal Tolerance Test (MMTT): Part A only

On the mornings of the MMTT days (Overnight Baseline, Day 85, and Day 162), a subset of subjects enrolled in Part A prior to the Protocol Amendment #1 will be awakened by 7:00 am after an overnight fast of at least 8 hours. During the 8 hour overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in the case of hypoglycemia. Prior to and during the MMTT, the subjects will be at rest (sitting or lying down), with quiet activities such as reading or TV watching.

At Time 0, subjects will begin a standard meal for the MMTT. As they will be on an IV infusion of insulin, the rate of insulin infusion should be continued at the time 0 rate for the duration of the MMTT and arginine stimulation procedure. No bolus insulin be given prior to the MMTT.

For all other subjects enrolled or are ongoing at the time of the Protocol Amendment #1, the overnight admissions to the CRU at Baseline, Week 13 and Week 24 will not occur. These subjects will return to the CRU in the morning to complete the MMTT at Baseline and Week 13 visits, after an 8 hour overnight fasting at home. Fasting plasma glucose samples will also be collected, prior to the administration of the MMTT. For all subjects, fasting blood glucose should be 80-180 mg/dl. During the overnight fasting at home, subject can drink juice or take glucose tabs if hypoglycemic. No rapid acting insulin should be taken within 4 hours prior of the MMTT.

For subjects on insulin pumps: The insulin pump will continue until the completion of the MMTT.

For subjects on insulin injections with basal insulin given at night: Subjects can take their last dose of long acting insulin in the evening prior to the Baseline Visit.

For subjects on insulin injections with basal insulin given in the morning: Subjects will take their normal AM dose of basal insulin in the morning a day prior to the Baseline Visit, as well as on the morning of the MMTT.

The standard meal consists of 2 servings [8 fluid ounces (237 mL)/ serving] of liquid Ensure Plus containing a total of 700 kcal. The total mixed-meal serving will be broken up into 4 equal portions, and each portion will be served every 5 minutes. The entire meal should be consumed within a 15-minute period. Water and non-caffeinated, calorie-free beverages may be consumed ad libitum. During the MMTT, C-peptide, glucagon, insulin, GLP-1 (active and total), and glucose concentrations will be measured 10 minutes before (time-10) and just before (time 0) initiating mixed-meal ingestion and at 30, 60 and 120 minutes after initiating mixed meal ingestion. Stimulated C-peptide will be measured with the ultra-sensitive C-peptide kit from Mercodia.

Arginine Challenge Test: Part A only (prior to Amendment #1)

For a subset of subjects enrolled in Part A prior to Protocol Amendment #1, the arginine challenge test will be performed during the Overnight Baseline Visit, Day 85, and Day 162 immediately after the completion of the MMTT. The 120 minute time-point completion for the preceding MMTT, will also serve as time zero (0) for the Arginine Challenge Test.

An intravenous injection of 5 g of arginine (given as 50 mL volume of a 10% arginine HCl solution) will be administered over 30 to 60 seconds, with time 0 set halfway through the arginine injection. Samples for plasma glucose, glucagon, C-peptide, and GLP-1 will be collected from the contralateral arm at 2, 3, 4, 5, 7, and 10 min after the arginine injection. After the last draw at 10 minutes, the IV insulin infusion can be discontinued and subjects will be instructed on how to resume their usual insulin therapy per protocol.

For all other subjects enrolled in Part A or are ongoing at the time of the Protocol Amendment #1, the arginine challenge test will not be conducted.

Seven-Point Blood Glucose Profile

Seven-point blood glucose profiles (measuring glucose via finger stick, at the following times of day: before each meal, 2 hours after each meal, and at bedtime) will be performed for periods of three consecutive days. During the Lead-In Period, subjects will record their seven-point blood glucose (BG) profile over a single period of 3 consecutive days either, prior to the Baseline Visit (subjects participating in Part A) or prior to the Day 1 Visit (subjects participating in Part B). During the 12 Week Dosing Period and 12 Week Follow-up Period, seven-point BG profiles will be performed over the three consecutive days following Dose 4 (Study Days 23 – 25), Dose 8 (Study Days 51 – 53), and Dose 12 (Study Days 79 – 81), and during Weeks 16 and 20 of the Follow-up Period.

Ketone Finger-Stick

Subjects will be provided with a blood ketone meter and blood ketone test strips in order to measure blood ketone readings via finger-stick method. For subjects in Part A only, blood ketone readings will be performed in the morning and collected by the subject while in a fasted state, prior to the subject's morning meal. During the 12-Week Dosing Period (starting on Day 1 and continuing through the completion of Week 12) the blood ketone readings will be performed 3 days a week – on an alternate day basis starting on Day 1 (e.g. Week 1: Study days 1, 3, 5 or on Mondays, Wednesdays, and Fridays), and once weekly during the 12-Week Follow-up Period. Subjects will be instructed to contact the investigator if they have positive ketones and blood sugars > 300mg/dL. Subjects enrolled in Part B will also be provided with a blood ketone meter and blood ketone test strips to be used as needed, however, there is no required collection schedule. Subjects in Part B will be advised to perform blood ketone readings via finger-stick method when they feel ill, or symptomatic of ketoacidosis, or as instructed by the investigator.

The blood ketone results will be automatically recorded in the combination blood glucose /blood ketone meter. **Please Note:** Data from the blood glucose / blood ketone meter will need to be collected and reviewed by the investigator and/or study staff at each study visit.

Readings will be made by gently inserting the test strip into the meter, after which the subject will apply a small drop of blood from the finger to the white target area at the end of the test strip. The blood is then drawn into the test strip, at which time the blood ketone value will be displayed on the blood ketone test meter. Additionally, serum ketones and free

fatty acids will be measure during each weekly visit during the treatment period, as outlined in the Schedule of Assessments (Appendix A).

Quality of Life (QOL) Questionnaire

The Type 1 – Diabetes Distress Scale (T1-DDS) and WHO-5 Well-Being Index scales (Appendix D) will be provided to the subject at the beginning of the following study visits: Overnight Baseline Visit and Days 85 and 161(EOS) visits.

The T1-DDS is a validated survey instrument that assesses diabetes-related emotional distress and includes 28 items. Thinking back over the past month, the subject will be asked to indicate the degree to which each of the items may have been a problem.

The WHO-5 Well-Being Index scale includes five statements in which the subject will need to rate based on how the subject has been feeling over the last two weeks.

Blood Volume

It is anticipated that subjects enrolled in this study will agree to provide whole blood for safety, PK, and PD assessments during their participation in this study as listed in Table 7-1:

Table 7-1: Total Blood Volume for samples collected prior to Protocol Amendment #1, for subjects participating in Part A

Procedure	Volume per Collection (mL)	Number of Collections	Total Volume (mL)
Safety (chemistry + hematology)	5	9	45
Fasting Plasma Glucose	2	15	30
Fasting Lipid Panel	5	9	45
Serum PK sample collection	4	6	24
Serum FSH levels (women only) Φ	5	1	5 Φ
HbA1c	6	4	24
Plasma Glucose via YSI	0.75	27	20
MMTT (glucose & insulin)	40	3	120
GLP-1 (active & total), Glucagon, Plasma insulin and C-peptide	4	6	24
Anti-REMD-477 Ab sample collection *	10 (first) / 5	3	20
Exploratory biomarker collection	30	3	90
Serum Ketones & free fatty acids	1.5	15	22.5
TOTAL**			**464.5** / **469.5Φ**

* First collection is 10 mL, subsequent collections are 5 mL.
** Volume to be collected over approximately 238 days.

Table 7-2: Total Blood Volume for samples collected under Protocol Amendment #1, for subjects participating in Part A

Procedure	Volume per Collection (mL)	Number of Collections	Total Volume (mL)	
Safety (chemistry + hematology)	5	9	45	
Fasting Plasma Glucose	2	15	30	
Fasting Lipid Panel	5	9	45	
Serum PK sample collection	4	6	24	
Serum FSH levels (women only) Φ	5	1	5 Φ	
HbA1c	6	4	24	
Plasma Glucose via YSI	NA	NA	NA	
MMTT (glucose & insulin)	40	2	80	
GLP-1 (active & total), Glucagon, Plasma insulin and C-peptide	4	6	24	
Anti-REMD-477 Ab sample collection *	10 (first) / 5	3	20	
Exploratory biomarker collection	30	3	90	
Serum Ketones & free fatty acids	1.5	15	22.5	
TOTAL **			**404.5**	**409.5Φ**

* First collection is 10 mL, subsequent collections are 5 mL.
** Volume to be collected over approximately 238 days.

Table 7-3: Total Blood Volume for samples collected under Protocol Amendment #2, for subjects participating in Part B

Procedure	Volume per Collection (mL)	Number of Collections	Total Volume (mL)
Safety (chemistry + hematology)	5	9	45
Fasting Plasma Glucose	2	15	30
Fasting Lipid Panel	5	9	45
Serum PK sample collection	4	6	24
Serum FSH levels (women only) Φ	5	1	5 Φ
HbA1c	6	5	30
GLP-1 (active & total), Glucagon, Plasma insulin and C-peptide	4	6	24
Anti-REMD-477 Ab sample collection *	10 (first) / 5	3	20
Exploratory biomarker collection	30	3	90
Serum Ketones & free fatty acids	1.5	15	22.5
Liver Injury Biomarkers	10	5	50
TOTAL**			**380.5** / **385.5Φ**

* First collection is 10 mL, subsequent collections are 5 mL.
** Volume to be collected over approximately 224 days.

Laboratory Safety Tests

Blood and urine samples for laboratory safety tests (clinical chemistry, hematology, and urinalysis) will be collected according to the Schedule of Assessments (Appendix A).

The date and time of blood and urine collection will be recorded in the subject's source documentation. The tests will be analyzed using standard procedures. White blood cell differentials will be reported in absolute counts.

All laboratory tests must be reviewed by the Principal Investigator or qualified designee prior to the subject receiving each dose. Additional safety laboratory assessments may be performed if clinically indicated.

The following analytes will be tested:

Chemistry

Albumin	Blood urea nitrogen (BUN)
Calcium	Chloride
Glucose	Phosphorus
Potassium	Serum creatinine
Magnesium	Sodium
Bicarbonate	Uric acid
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)
Cholesterol	Lactate dehydrogenase (LDH)
Alkaline phosphatase (ALP)	Total bilirubin
Total protein	Direct bilirubin
HDL, LDL, Triglycerides	Total globulin

Hematology

Red blood cells (RBC) Hemoglobin (Hgb) Hematocrit (Hct) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) corpuscular hemoglobin concentration (MCHC) count RDW	White blood cells (WBC) Differential count: • Segmented neutrophils • Band cells • Eosinophils Mean • Basophils Platelet • Lymphocytes • Atypical lymphocytes

Miscellaneous

Serum Ketones
Free Fatty Acids

Urinalysis

Specific gravity	pH
Blood	Protein
Glucose	Ketones
Bilirubin	Urobilinogen
WBC	RBC
Epithelial Cells	Bacteria
Casts	Crystals

Urine Drug Test

Amphetamine	Cocaine
Opiates	Benzodiazepines
Barbiturates	Methadone
	Alcohol/Ethanol

Other Screening Laboratory Tests

At screening, a spot urine collection will be evaluated for presence of alcohol and drugs of abuse listed above. Urine will also be collected at the Baseline Visit, Day 29, and Day 162 and will be evaluated for the analytes listed above (urine drug test). The results will be documented in the source records, but not captured on the respective eCRF page.

Next, serum will be collected for a follicle stimulating hormone (FSH) test (for women who are at least 1 year postmenopausal) at screening. Women of non-childbearing potential must have FSH levels ≥ 40 IU/mL.

Other Serum Laboratory Testing

Blood samples to measure GLP-1, glucagon, HbA1c, plasma insulin, serum ketones, free fatty acids (FAA), and C-peptide will be obtained after an overnight fast of 8 hours, or at time points outlined in the Schedule of Assessment (Appendix A). Please refer to laboratory

manual for detailed collection, handling and shipping procedures for GLP-1, glucagon, serum ketones, FFA, insulin and C-peptide samples.

Anti-REMD-477 Antibody sample collection

Subjects will have blood samples drawn for antibody determination on Days 1 (pre-dose), 85, and 162/EOS.

Sample collection, serum processing, and shipping instructions will be provided in a separate lab manual.

Blood Collection for Serum Pharmacokinetics Analysis

Blood will be collected and assayed for REMD-477 serum concentration. Baseline measurements will be collected just before dosing on Day 1. Samples will be drawn on Days 1, 8, 29, 57, 85, and 106. If a sample draw occurs during a dosing day, the sample should be collected pre-dose. Time of PK sample collection will be recorded in hours and minutes.

Sample collection, processing, storage and shipping instructions will be provided in a separate lab manual.

Exploratory Biomarker Collection

Blood samples for biomarker purposes will be collected pre-dose on Day 1, Day 85, and Day 162 (EOS Visit). These samples may be used in future analyses in an effort to identify novel biomarkers for diabetes and glucagon-related pathways.

Liver Injury Biomarker Collection

For subjects enrolled in Part B, blood samples to measure biomarkers of liver injury will be collected pre-dose on Day 1, Day 29, Day 57, Day 85, and Day 106. Sample collection, serum processing, and shipping instructions will be provided in a separate lab manual. These biomarkers will include but are not limited to cytokeratin 18 (CK-18) M65, CK-18 M30, high mobility group protein B1 (HMGB1), and glutamate dehydrogenase.

Magnetic Resonance Imaging – Proton Density Fat Fraction (MRI-PDFF)

For a subset of subjects in Part B only who consent to the procedure, liver MRI-PDFF 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.

MRI-PDFF will only be performed at centers with equipment and software capable of conducting the scans. Subjects for whom an MRI is contraindicated (e.g., including but not limited to artificial heart valves or pacemakers), will be not enrolled to this sub-study.

Baseline and post-treatment MRI-PDFF will be performed to assess changes in liver fat content. This technique utilizes a gradient echo sequence with low flip angle to minimize the T_1 bias, and it acquires multiple echoes at echo times at which fat and water signals are nominally in-phase or out-of-phase relative to each other. Data obtained at each of the echo times are passed to a nonlinear least-squares fitting algorithm that estimates and corrects T_2* effects, models the fat signal as a superposition of multiple frequency components, and estimates fat and water proton densities from which the fat content is calculated.

Imaging PDFF will be recorded in regions of interest (ROIs) 300 to 400 mm^2 in area placed on the PDFF parametric maps, avoiding blood vessels, bile ducts, and artifacts. To assess longitudinal changes in fat content, multiple co-localized ROIs will be placed in each of the liver segments on the baseline and follow-up MRI exams.

MRI-PDFF scans may be sent to a central imaging vendor for independent evaluation of liver fat content. The central radiologist should not have access to the treatment assignments or knowledge of whether the scans are performed at baseline or post-treatment for each patient.

Liver FibroScan®

A FibroScan® is a specialized ultrasound machine that measures fibrosis (scarring) and steatosis (fatty change) in the liver. For a subset of subjects in Part B only, sites that have access to a FibroScan® may elect to perform a FibroScan® prior to dosing on Day 1 (or up to 7 days before Day 1, after all other inclusion and exclusion criteria have been met) and on Day 85 (+/- 2 days) of Week 13. Scans will also be performed at the first occurrence of serum AST or ALT increase >3 xULN.

8. REMOVAL AND REPLACEMENT OF SUBJECTS

Removal of Subjects

Subjects have the right to withdraw fully or partially from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. The Principal Investigator and REMD Biotherapeutics also have the right to withdraw a subject from the study at any time for any reason.

Withdrawal of full consent for a study means that the subject does not wish to receive further investigational treatment and does not wish to or is unable to continue further study participation. Any subject may withdraw full consent to participate in the study at any time during the study. The Principal Investigator will discuss with the subject the most appropriate way to withdraw to ensure the subject's health.

Withdrawal of partial consent means that the subject does not wish to take investigational product any longer but is still willing to collaborate in providing further data by continuing on study (e.g., participate in all subsequent study visits or procedures). Subjects may decline to continue receiving investigational product at any time during the study. These subjects, as well as those who have stopped receiving investigational product for other reasons (e.g., Principal Investigator or sponsor concern) should continue the schedule of study observations.

Subjects who early terminate the study during the 12-week treatment period will be monitored for 12-weeks after the last injection of study drug (REMD-477 or placebo).

The reason for withdrawal will be recorded on the end-of-study eCRF page. If the subject is withdrawn due to an adverse event, the Principal Investigator will arrange for the subject to have follow-up visits until the adverse event has resolved or stabilized.

Reasons for removal from investigational product or observation might include:

- withdrawal of consent
- administrative decision by the investigator or REMD Biotherapeutics
- pregnancy (report on Pregnancy Notification Worksheet)
- pregnancy in female partner of a male subject during treatment and up to EOS (report on Pregnancy Notification Worksheet)
- ineligibility
- significant protocol deviation

- subject noncompliance
- adverse event (may include disease progression; report on adverse event eCRF)

Replacement of Subjects

Randomized subjects who do not receive REMD-477 or matching placebo may be replaced.

Subjects who receive study drug and do not complete all study procedures as per protocol may be replaced. A replacement subject will be assigned the same dose, route, and treatment group of the replaced subject. However, subjects who are removed from the study as a result of investigational drug related or possibly related adverse events (after receiving study medication) may or may not be replaced, per Investigator's discretion.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

Adverse Events

An adverse event is defined in the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment.” (ICH E6:1.2)

This definition of adverse events is broadened in this study to include any such occurrence (e.g., sign, symptom, or diagnosis) or worsening of a pre-existing medical condition from the time that a subject is admitted to the clinical research unit, CRU, for the Overnight Baseline Visit or returns to the CRU for the Baseline Visit.

This definition of adverse events also includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., cancer, diabetes, migraine headaches, gout) has increased in severity, frequency, or duration of the condition or an association with significantly worse outcomes.

Interventions for pretreatment conditions (e.g., elective cosmetic surgery) or medical procedures that were planned before study enrollment are not considered adverse events.

The Principal Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a change from values before the study. In general, abnormal laboratory findings without clinical significance (based on the Principal Investigator's judgment) should not be recorded as adverse events; however, laboratory value changes requiring therapy or adjustment in prior therapy are considered adverse events.

Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that:

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- other significant medical hazard

A hospitalization meeting the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. Any adverse event that does not meet one of the definitions of serious (e.g., emergency room visit, outpatient surgery, or requires urgent investigation) may be considered by the investigator to meet the “other significant medical hazard” criterion for classification as a serious adverse event.

Reporting Procedures for All Adverse Events

The Principal Investigator is responsible for ensuring that all adverse events observed by the Principal Investigator or reported by subjects are collected and recorded in the subjects’ medical records, in the eCRF, and, for serious adverse events, on the serious adverse event report (SAER) form. These adverse events will include the following:

- All serious adverse events that occur after the subject has signed the informed consent form.
- All non-serious adverse events that occur after treatment with investigational product.

The following adverse event attributes must be assigned by the Principal Investigator: adverse event diagnosis or syndrome(s) (if known, signs or symptoms if not known); event description (with detail appropriate to the event); dates of onset and resolution; severity; assessment of relatedness to investigational product; and action taken. The Principal Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRF pages.

If applicable, the relationship of the adverse event to the investigational product will be assessed by means of the question: “Is there a reasonable possibility that the event may have been caused by the investigational product (i.e., cannot be ruled out)?” The Principal Investigator should respond to this question with either Yes or No.

If a serious adverse event occurs before randomization to investigational product, the relationship of the adverse event to study screening is to be assessed by means of a similar question: “Is there a reasonable possibility that the event may have occurred because of study related activity or procedure?” The Principal Investigator should respond to this question with either Yes or No. If the answer is "Yes", record what activity or procedure is suspected.

The CTCAE V. 4.03 will be used in this study.

Medically significant adverse events considered related to the investigational product by the Principal Investigator or the sponsor will be followed until resolved or considered stable.

It will be left to the Principal Investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-study assessment and be under medical supervision until symptoms cease or the condition becomes stable.

Adverse Event Severity Grade

Each adverse event must be assigned a Grade, which refers to the severity of the adverse event. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event on this general guideline:

- Grade 1 – Mild AE
- Grade 2 – Moderate AE
- Grade 3 – Severe AE
- Grade 4 – Life-threatening or disabling AE
- Grade 5 – Death related to AE.

Serious Adverse Event Reporting Procedures

Serious adverse events will be collected throughout the study period, beginning with the signing of the informed consent through 30 days after the last dose of investigational product or end of the study (including the follow-up period), whichever is longer. Serious adverse events also will be collected if they occur >30 days after the last dose of investigational product or after the end of the study AND is thought to be possibly related to investigational product.

All serious adverse events must be reported to REMD Biotherapeutics or designated CRO within 24 hours of discovery or notification of the event. Initial serious adverse event information and all amendments or additions must be recorded on a Serious Adverse Event Report Form and faxed to REMD Biotherapeutics or designated CRO. Relevant medical records should be faxed to REMD Biotherapeutics or designated CRO as soon as they become available; autopsy reports should be provided for deaths if available.

To comply with local or regional serious adverse event reporting regulations, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded before submission to regulatory authorities by REMD Biotherapeutics or designated CRO. Determination of expectedness for REMD Biotherapeutics or designated CRO will be based on the contents of the Investigator's Brochure for investigational products.

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be included in the initial or follow-up Serious Adverse Event Report Form as well as the End of Study eCRF page.

The Principal Investigator should notify the appropriate IRB or ethics committee of serious adverse events occurring at the CRU and other adverse event reports received from REMD Biotherapeutics or designated CRO, in accordance with local procedures and statutes.

10. STATISTICAL CONSIDERATION

Study Endpoints, Subsets, and Covariates

Primary Endpoints:

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

Secondary Endpoints:

- Change from baseline at Week 13 in fasting glucose and glucose AUC after the MMTT – for 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).
- Subject incidence of adverse events and clinically relevant changes in medical history, physical examination, laboratory safety values, and ECGs.
- Incidence of hypoglycemic events.
- Change from baseline at Week 13 in HbA1c.
- Proportion of subjects who achieve HbA1c reduction of ≥ 0.4%.
- Change from baseline at 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 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 challenge – in Part A only.
- REMD-477 plasma concentrations and incidence of anti-REMD-477 antibody formation.

Exploratory Endpoints:

- Change from baseline at Week 13 in body weight.
- Change from baseline in QOL score at 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)

Sample Size Considerations:

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 group. Based on 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.

Access to Individual Subject Treatment Assignments

All investigators and all staff associated with the study conduct will be blinded, with the exception of the unblinded pharmacist and biostatistician preparing the randomization schedule.

At least one pharmacy staff member at each study site is unblinded to distribute, document, and track investigational drug, and is responsible for unblinding the treatment assignment when needed for safety reasons. With the exception of the unblinded pharmacist, and another member of the site staff not involved in the conduct of study, who will have access to an individual's treatment during the conduct of the study, a subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject or may impact the safety of subjects currently enrolled. Unblinding for any other reason will be considered a protocol violation. A subject's treatment assignment should only be unblinded by the Principal Investigator and/or by REMD Biotherapeutics medical monitor or clinical operations director.

The Principal Investigator is strongly encouraged to contact the REMD Biotherapeutics study manager before unblinding any subject's treatment assignment, but must do so within one working day after the event. The unblinding must be documented in the subject's source records and also noted on the appropriate eCRF page. Dose escalation will proceed after a review of safety data by REMD Biotherapeutics medical monitor or clinical operations director.

Interim Analysis

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 Covance and REMD study teams; Investigators and subjects will remain blinded. The preliminary analyses may be shared with the Investigators in an aggregate form such that blinding is maintained.

Planned Methods of Analysis

General Approach/Considerations

Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges while categorical data will be summarized using frequency counts and percentages.

Analysis of Key Study Endpoints

An analysis of variance will be used to evaluate post intervention changes in daily insulin use between treatment groups.

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.

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, 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, then the corresponding test is considered to have reached statistical significance.

Step 2: If at least 1 of the 2 doses of REMD-477 is found to be superior to placebo, then the 2 doses of REMD-477 will be compared using the same significance level as that used to claim significance of either dose of REMD-477.

Preliminary analyses of variance will be performed to confirm that baseline characteristics of participants are similar in the groups. If necessary, analyses of covariance will be performed to adjust for any pre-intervention difference between 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.

Descriptive statistics will be provided for selected demographics, safety and PD data. Descriptive statistics on continuous measurements will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages.

For the product of the ratio of average glucose (Week 12/Baseline) and ratio of average insulin use (Week 12/Baseline), glucose AUC after MMTT, C-peptide AUC after MMTT and arginine challenge test (for a subset of subjects in Part A who were enrolled prior to Protocol Amendment #1), fasting glucose, insulin, C-peptide, GLP-1, and glucagon, a repeated measures analysis of covariance will be performed, as well as before and after treatment analysis.

For comparison of proportion of subjects that achieve HbA1c reduction of ≥ 0.4% in the REMD-477 and placebo groups, chi-square test will be conducted.

For a subset of subjects in Part B, the change in hepatic fat content from baseline will be calculated for each subject and the mean change will be calculated for each treatment arm.

Study Disposition and Demographic Data

The number of subjects who receive investigational product and complete the study will be summarized. A list of subjects who withdraw early will be provided. It will include the reason and timing of the withdrawal. Similarly, the reason any subject is excluded from an analysis set will also be provided. In addition, significant known protocol deviations will be noted for individual subjects.

Age, race, sex, height, and weight will be summarized for all the subjects receiving investigational product using descriptive statistics.

Population Pharmacokinetics

Serum REMD-477 concentrations will be determined using a validated assay. A population

PK analysis will be performed from REMD-477 concentrations evaluated on Days 1, 8, 29, 57, 85, and 106.

Safety Analysis

Adverse Events

All subjects who receive at least one dose of REMD-477 or placebo will be included in the safety analyses. The number of subjects reporting treatment-emergent adverse events will be determined overall, by preferred term, and by system organ class according to the current MedDRA terminology. The number and percentage of subjects reporting adverse events will be evaluated for each treatment and will also be tabulated by relationship to study drug.

Adverse events resulting in treatment discontinuation will be identified.

Vital Signs

Vital signs will be listed and reviewed for each subject. Summaries of heart rate and blood pressure data over time and change from baseline will be provided. Depending on the size and scope of change in other vital signs, summaries may be provided for this data.

Heart rate and blood pressure will be analyzed with a repeated measures analysis of covariance. Dependent variables will be treatment, time and the treatment by time interaction. The baseline value will serve as a covariate. Subject will be used as a random effect. The least square mean of each treatment will be presented for each time. 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 presented at each time.

Electrocardiogram

All on-study ECG data will be listed and may be plotted. The Bazett's (QTcB) and Fridericia's (QTcF) QT corrections will be computed.

Subjects will be categorized into the following groups per their maximum change from baseline in QTcF and QTcB:

- ≤ 30 msec
- > 30 – 60 msec
- > 60 msec

The number of subjects in each group will be summarized for each dosing group.

Subjects will also be categorized into the following groups per their maximum post baseline QTcF and QTcB

- ≤ 450 msec
- > 450 – 480 msec
- > 480 – 500 msec
- > 500 msec

The number of subjects in each group will be summarized for each dosing group.

Summaries over time and/or changes from baseline over time will also be provided. The relationship between serum concentration of REMD-477 and change from baseline in QTcF and QTcB will be explored graphically; if both QTcF and QTcB exhibit similar relationships, only the QTcF graph will be provided.

The change from baseline of QT interval will be analyzed with a repeated measures analysis of covariance. Dependent variables will be treatment, time and the treatment by time interaction. The change from baseline of the RR interval will serve as a covariate. Subject will be used as a random effect. The estimated treatment mean when change in RR interval equals 0 will be presented for each time. Also, the difference from placebo, the 90% confidence interval of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be presented at each time.

A similar analysis will be performed using the change from baseline of QTcF. Dependent variables will be treatment, time, and the treatment by time interaction. The baseline QTcF will serve as a covariate. Subject will be used as a random effect. Treatment least square means will be presented for each time. Also, the difference from placebo, the 90% confidence interval of the difference from placebo, and p-value associated with the null-hypothesis of no difference will be presented at each time.

Clinical Laboratory

Hematology, biochemistry and urinalysis data will be listed and reviewed for each subject. Values outside the normal laboratory reference range will be flagged as high or low on the listings.

REMD-477 Antibody Assessment

Neutralizing and non-neutralizing antibody titers will be assessed at pre-dose and at various time points throughout the study including EOS. Antibody data will be listed for each subject.

11. INVESTIGATIONAL PRODUCT

REMD – 477

REMD-477 will be manufactured, filled and packaged by certified contract manufacturing organizations (CMO) and distributed using a GCP-compliant clinical trial drug distribution procedures. REMD-477 is supplied as single-use glass vials. REMD-477 is formulated with 10mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20 at a protein concentration of 70 mg/mL.

The formulation of placebo is 10 mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20.

Investigational product details including labeling, storage, preparation, etc. are provided in the Pharmacy Guide (Appendix B).

Access to Treatment Assignments

In this study, a designated pharmacist or designee from the CRO and one from each CRU will be identified as unblinded pharmacists and will be responsible for preparing the appropriate treatment based on the randomization schedule. The CRO's unblinded statistician and unblinded pharmacists at all sites will have access to the randomization schedule, and will be responsible for securing the schedule and any unblinded pharmacy records in a private location under lock and key. Access to the randomization schedule or unblinded pharmacy records will be limited to the unblinded statistician and pharmacists (or a qualified designee). CRU site staff including the Principal Investigators will not have any access to the randomization schedule or unblinded pharmacy records at any time during the course of the study.

The unblinded pharmacists will prepare individual subject doses labeled with the individual subject identification number and randomization number, date and time prepared and the initials of the preparer. The unblinded pharmacists will ensure that REMD-477 or matching placebo dispensed to the subjects is labeled such that treatment identity cannot be determined.

A subject's treatment assignment should only be unblinded by the Principal Investigator and/or by REMD Biotherapeutics medical monitor or clinical operations director when knowledge of the treatment is essential for the further management of the subject or may

impact the safety of subjects currently enrolled. Unblinding for any other reason will be considered a protocol violation. The Principal Investigator is strongly encouraged to contact the REMD Biotherapeutics or designated CRO study manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event and must document the unblinding in the subject's source records, and in the Pharmacy Binder. If blind break envelopes are provided, all blind break envelopes must be accounted for and returned to the monitor at the end of the study. Any instance of unblinding will be reported in the clinical study report.

Compliance in Investigational Product Administration

Multiple SC doses of placebo, 35 mg REMD-477, or 70 mg REMD-477 will be administered at the CRU by a qualified staff member on Day 1, followed with repeated weekly doses for an additional 11 weeks. Each SC dose will be administered to the subject's anterior upper abdominal wall and its volume will be no more than 1 mL. When REMD-477 or matching placebo is dispensed, the Principal Investigator or responsible person will determine the level of compliance with the administration of the investigational product.

12. REGULATORY OBLIGATIONS

Informed Consent

An initial generic informed consent form (template) is provided as a separate document for the Principal Investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the REMD Biotherapeutics or designated CRO to the Principal Investigator. The written informed consent document should be prepared in the language(s) of the intended subject population.

Before a subject's participation in the clinical study, the Principal Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The Principal Investigator is also responsible for asking the subject if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the Principal Investigator shall inform the subject's primary care physician of the subject's participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records and the study source document, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the Principal Investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Principal Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by

REMD Biotherapeutics or designated CRO before recruitment of subjects into the study and shipment of investigational product.

The Principal Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The Principal Investigator should notify the IRB of deviations from the protocol or serious adverse events occurring at the CRU and other adverse event reports received from REMD Biotherapeutics or designated CRO, in accordance with local procedures.

The Principal Investigator will be responsible for obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the Principal Investigator's reports and the IRB continuance of approval must be sent to REMD Biotherapeutics or designated CRO.

Pre-study Documentation Requirements

The Principal Investigator is responsible for forwarding the following documents to REMD Biotherapeutics or designated CRO for review before study initiation can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form
- Copy of the IRB approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of Principal Investigator and all co/subinvestigators
- IRB composition and/or written statement that IRB is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Signed study contract
- Completed FDA form 1572

Subject Confidentiality

The Principal Investigator must ensure that the subject's confidentiality is maintained:

- On the case report forms or other documents submitted to REMD Biotherapeutics or designated CRO, subjects should be identified by a subject study number only.
- On Serious Adverse Event forms submitted to REMD Biotherapeutics or designated CRO, subjects should be identified by their initials and a subject study number only.
- Documents that are not for submission to REMD Biotherapeutics or designated CRO (e.g., signed informed consent forms) should be kept in strict confidence by the Principal Investigator.

In compliance with federal regulations/ICH GCP Guidelines, it is required that the Principal Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Principal Investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

Investigator Signatory Obligations

Each clinical study report should be signed by the Principal Investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating Principal Investigator, identified by REMD Biotherapeutics or designated CRO, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of REMD Biotherapeutics. Agreement from the Principal Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval. The Principal Investigator **must** send a copy of the approval letter from the IRB to REMD Biotherapeutics or designated CRO.

REMD Biotherapeutics reserves the right to terminate the study according to the study contract. The Principal Investigator should notify the IRB in writing of the study's completion or early termination and send a copy of the notification to REMD Biotherapeutics or designated CRO.

Subjects may be eligible for continued treatment with investigational product by extension protocol or as provided for by the local regulatory mechanism. However, REMD Biotherapeutics reserves the unilateral right, at its sole discretion, to determine whether to supply the investigational product, and by what mechanism, after termination of the trial and before it is available commercially.

Study Documentation and Archive

The Principal Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to interact with study subjects or to make entries and/or corrections on case report forms will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, glucometer records, insulin diaries, microfiches, radiographs, and correspondence.

The Principal Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from REMD Biotherapeutics or designated CRO and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed case report forms, informed consent forms, and subject identification list;
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation, and all correspondence to and from the IRB and REMD Biotherapeutics;
- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between REMD Biotherapeutics and the Principal Investigator. Should the Principal Investigator wish to assign the study records to another party or move them to another location, he/she must notify REMD Biotherapeutics in writing of the new responsible person and/or the new location.

Study Monitoring and Data Collection

The REMD Biotherapeutics or designated CRO representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., case report forms and other pertinent data) provided that subject confidentiality is respected.

The REMD Biotherapeutics or designated CRO monitor is responsible for verifying the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from REMD Biotherapeutics or designated CRO's Clinical Quality Assurance Department (or designees). Inspection of site facilities (e.g., pharmacy, drug

storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Corrections to electronic forms will be automatically documented through the software's "audit trail".

To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at REMD Biotherapeutics or designated CRO. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and returned to REMD Biotherapeutics or designated CRO.

The principal investigator will sign and date the indicated places on the case report form. These signatures will indicate that the principal investigator inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.

The principal investigator signs only the Investigator Verification Form for all EDC studies.

REMD Biotherapeutics or designated CRO's clinical data management department will correct the database for the following CRF issues without notification to CRU site staff:

- clarifying "other, specify" if data are provided (e.g., race, physical exam)
- deletion of obvious duplicate data (e.g., same results sent twice with the same date but different clinical planned events—week 4 and early termination)
- addition of a leading zero to date and/or time entries
- deletion of leading and/or trailing spaces to adverse event or concomitant medication terms to facilitate uploading of coded files

Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. Consult the country- specific requirements for language requirements.

Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed

Consent provided to the Principal Investigator as a separate document. Depending on the type of study, subjects may be compensated for other inconveniences not associated with study-related injuries (e.g., child care costs).

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15. APPENDICES

Appendix A. Schedule of Assessments – Part A

Study Period (or Dose #)	Screen	Lead-In		Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8
Study Week	≤ 42 days		Baseline Visit	1		2	3	4	5	6	7	8
Study Day		2 to 4 Weeks	Day -8/-7 to Day -2/ -1	Pre-dose	1	8 ± 1	15 ± 1	22 ± 1	29 ± 1	36 ± 1	43 ± 1	50 ± 1
Informed consent	X											
Medical History [a]	X		X									
Physical examination	X		X						X			
Height (Screening only) & Body weight	X	X	X						X			
Urine pregnancy test (women); FSH [g]	X		X						X			
Urine drug/alcohol test	X		X						X			
12-lead ECG [b]	X		X						X			
Vitals (BP, RR, HR, T) [c]	X	X	X	X		X	X	X	X	X	X	X
Chemistry, Hematology, Lipid Panel, and Urinalysis	X		X			X	X		X		X	
Fasting (≥ 8-hr) plasma glucose [e]			X	X		X	X	X	X	X	X	X
Serum Ketones & Free Fatty Acids			X	X		X	X	X	X	X	X	X
Study Drug SC Administration					X	X	X	X	X	X	X	X
Seven-point blood glucose profile [d]		X						X				X
Unblinded Continuous Glucose Monitoring (CGM) [h]		X		←								→
Ketone finger-stick [j]				X	X	X	X	X	X	X	X	X
Daily insulin usage dairy [i]		X		X	X	X	X	X				X
Hourly plasma glucose via YSI [e]			X [l]									
Mixed Meal Tolerance Test (MMTT) [e]			X									
Arginine Challenge Test [e]			X [l]									
HbA1c	X		X									
Insulin, C-peptide, GLP-1, and Glucagon [e, f]			X						X			
Serum PK sample collection [f]				X		X			X			
Anti-REMD-477 Ab sample collection [f]				X								
Exploratory biomarker collection				X								
QOL Questionnaires [k]			X									
Overnight Admission [l]			X									
Con-Med monitoring	X	←										→
Adverse event monitoring			←									→

Footnote Key:

a. Medical history includes significant past medical events (e.g. prior hospitalizations or surgeries), a review of diabetes history and glycemic control, and any concurrent medical illnesses.

b. After the Screening Visit, 12-lead ECG to be performed in triplicate, approximately 1 min apart. When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

c. Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.

d. Seven-point blood glucose profile will measure glucose by finger stick over three consecutive days before and 2 hours after each meal, and at bedtime.

e. **For a subset of subjects enrolled prior to Protocol Amendment #1**: subjects should fast overnight for 8 hours prior to MMTT. During the overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia. For the Overnight Baseline Visit (OBV), Day 85 visit and Day 162 Visit, fasting plasma glucose samples will be collected on the morning following admission, prior to the administration of the MMTT and Arginine Challenge Tests. MMTT must be completed prior to the Arginine Challenge Test.

For ongoing or newly enrolled subjects at the time of Protocol Amendment #1: overnight admission to the CRU at Baseline, Week 13, and Week 24 will not occur. For these visits, subjects will still return to the CRU to complete all the study procedures outlined here in the Schedule of Assessments table – however, all assessments for that visit will be performed on a single day (*Baseline Visit*: Day -8 to Day -1; *Week 13 Visit*: performed on Day 85; and *Week 24 Visit*: performed on Day 162).

- **Note:** For ongoing or newly enrolled subjects at the time of Protocol Amendment #1, the MMTT will only be administered at the Baseline and Week 13 visits, after the subject completes an 8 hour overnight fast at home (the MMTT is no longer required at Week 24). No Arginine Challenge Tests or YSI assessments will be performed for these subjects.

f. Sample should be collected pre-dose on all dosing days.

g. FSH required at screening for post-menopausal women.

h. Unblinded CGM will be performed for two weeks during the Lead-in Period (completed prior to the OBV), and throughout the study Dosing and Follow-up Periods from Dose 1 through the End of Study Visit. For on-going or newly enrolled subjects in Part A at the time of Protocol Amendment #2, CGM data will be collected throughout the study from Dose 1 through the Day 85/Week 13 Visit, and CGM devices will be "unblinded". CGM data will be downloaded at the clinical research unit during scheduled site visits, as indicated in the Schedule of Assessments.

i. Subjects will be given insulin usage diaries during the Lead-in Period and at the beginning of Weeks 1 through 4, 8, 12, 16, and 20. For both weeks of the Lead-in Period and Weeks 1 through 4, daily insulin use (short-acting, long-acting, and infusional as applicable) will be collected over seven days. For Weeks 8, 12, 16, and 20, daily insulin will be collected over a period of 3 consecutive days within that respective week.

j. Blood ketones will be measured in the morning (prior to the subject's morning meal) 3 days a week – on an alternate day basis (e.g. Week 1: Study days 1, 3, and 5 or on Mondays, Wednesday, and Fridays) during the 12–Week Dosing Period (starting on Day 1 and continuing through the completion of Week 12), and once weekly throughout the Follow-up Period & EOS (Day 85 through Day 162) via finger-stick (strips for finger-stick measurement will be provided to the subjects). Subjects will be instructed to contact the investigator if they have positive ketones.

k. The *WHO-5 Well-Being Index* & *T1-DDS* QOL Questionnaires will be completed by the subjects at the OBV, Day 84, and Day 161.

l. No longer applicable for ongoing or newly enrolled subjects at time of Protocol Amendment #1.

Schedule of Assessments – Part A

Study Period (or Dose#)	Dose 9	Dose 10	Dose 11	Dose 12	Follow-up Period				EOS	
Study Week	9	10	11	12	13 [m]		16	20	24 [m]	
Study Day	57 ± 1	64 ± 1	71 ± 1	78 ± 1	84 ± 2	85 ± 2	106 ± 2	134 ± 2	161 ± 2	162 ± 2
Informed consent										
Medical History [a]										
Physical examination					X					X
Body weight	X				X		X	X		X
Urine pregnancy test (women); FSH [g]	X				X					X
Urine drug/alcohol test										X
12-lead ECG [b]	X		X			X				X
Vitals (BP, RR, HR, T) [c]	X	X	X	X	X	X	X	X	X	X
Chemistry, Hematology, Lipid Panel, and Urinalysis	X					X				X
Fasting (≥ 8-hr) plasma glucose [e]	X	X	X	X		X				X
Serum Ketones & Free Fatty Acids	X	X	X	X			X	X		
Study Drug SC Administration	X	X	X	X						
Seven-point blood glucose profile [d]				X			X	X		
Unblinded Continuous Glucose Monitoring (CGM) [h]	◄	———	———	———	———	———	———	———	———	►
Daily (or Weekly) Ketone finger-stick [j]	X	X	X	X			X	X		
Daily insulin usage diary [i]				X			X	X		
Hourly plasma glucose via YSI [e]					X [l]	X [l]			X [l]	X [l]
Mixed Meal Tolerance Test (MMTT) [e]						X				X [l]
Arginine Challenge Test [e]						X [l]				X [l]
HbA1c						X				X
Insulin, C-peptide, GLP-1, and Glucagon [e, f]	X					X	X			X
Serum PK sample collection [f]	X					X	X			
Anti-REMD-477 Ab sample collection [f]						X				X
Exploratory biomarker collection						X				X
QOL Questionnaires [k]					X				X	
Overnight Admission [l]					◄	———	———	———	◄	——— ►
Con-Med monitoring	◄	———	———	———	———	———	———	———	———	►
Adverse event monitoring	◄	———	———	———	———	———	———	———	———	►

Footnote Key:

a. Medical history includes significant past medical events (e.g., prior hospitalizations or surgeries), a review of diabetes history and glycemic control, and any concurrent medical illnesses.

b. After the Screening Visit, 12-lead ECG to be performed in triplicate, approximately 1 min apart. When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

c. Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.

d. Seven-point blood glucose profile will measure glucose by finger stick over three consecutive days before and 2 hours after each meal, and at bedtime.

e. **For a subset of subjects enrolled prior to Protocol Amendment #1**: subjects should fast overnight for 8 hours prior to the MMTT. During the overnight fast, plasma glucose via YSI will be measured hourly, and subjects will be allowed to receive juice by mouth, in case of hypoglycemia. For the Overnight Baseline Visit (OBV), Day 85 visit and Day 162 Visit, fasting plasma glucose samples will be collected on the morning following admission, prior to the administration of the MMTT and Arginine Challenge Tests. MMTT must be completed prior to the Arginine Challenge Test.

For ongoing or newly enrolled subjects at the time of Protocol Amendment #1: overnight admission to the CRU at Baseline, Week 13, and Week 24 will not occur. For these visits, subjects will still return to the CRU to complete all the study procedures outlined in the Schedule of Assessment table – however, all assessments for that visit will be performed on a single day (*Baseline Visit:* Day -8 to Day -1*; Week 13 Visit*: performed on Day 85*; and Week 24 Visit:* performed on Day 162).

- **Note:** For ongoing or newly enrolled subjects at the time of Protocol Amendment #1, the MMTT will only be administered at the Baseline and Week 13 visits, after the subject completes an 8 hour overnight fast at home (the MMTT is no longer required at Week 24). No Arginine Challenge Tests or YSI assessments will be performed for these subjects.

f. Sample should be collected pre-dose on dosing days.

g. FSH required at screening for post-menopausal women.

h. Unblinded CGM will be performed for two weeks during the Lead-in Period (completed prior to the OBV), and throughout the study Dosing and Follow-up Periods from Dose 1 through the End of Study Visit. For on-going or newly enrolled subjects in Part A at the time of Protocol Amendment #2, CGM data will be collected throughout the study from Dose 1 through the Day 85/Week 13 Visit, and CGM devices will be "unblinded". CGM data will be downloaded at the clinical research unit during scheduled site visits, as indicated in the Schedule of Assessments.

i. Subjects will be given insulin usage diaries during the Lead-in Period and at the beginning of Weeks 1 through 4, 8, 12, 16, and 20. For both weeks of the Lead-in Period and Weeks 1 through 4, daily insulin use (short-acting, long-acting, and infusional as applicable) will be collected over seven days. For Weeks 8, 12, 16, and 20, daily insulin will be collected over a period of 3 consecutive days within that respective week.

j. Blood ketones will be measured in the morning (prior to the subject's morning meal) 3 days a week – on an alternate day basis (e.g. Week 1: Study days 1, 3, and 5 or on Mondays, Wednesday, and Fridays) during the 12–Week Dosing Period (starting on Day 1 and continuing through the completion of Week 12), and once weekly throughout the Follow-up Period & EOS (Day 85 through Day 162) via finger-stick (strips for finger-stick measurement will be provided to the subjects). Subjects will be instructed to contact the investigator if they have positive ketones.

k. The *WHO-5 Well-Being Index* & *T1-DDS* QOL Questionnaires will be completed by the subjects at the OBV, Day 84, and Day 161.

l. No longer applicable for ongoing or newly enrolled subjects at time of the Protocol Amendment #1.

m. **For ongoing or newly enrolled subjects at time of the Protocol Amendment #1**: overnight admission to the CRU at Week 13 & Week 24 will not occur.

For these visits, Week 13 procedures will be performed on Day 85, and Week 24 procedures will be performed on Day 162.

Appendix A. Schedule of Assessments – Part B

Study Period (or Dose #)	Screen	Lead-In	Dose 1		Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8
Study Week	≤ 42 days		1		2	3	4	5	6	7	8
Study Day		1 to 2 Weeks	Baseline/ Pre-dose	1	8 ± 1	15 ± 1	22 ± 1	29 ± 1	36 ± 1	43 ± 1	50 ± 1
Informed consent	X										
Medical History [a]	X		X								
Physical examination	X		X					X			
Height (Screening only) & Body weight	X	X	X					X			
Urine pregnancy test (women); FSH [f]	X		X					X			
Urine drug/alcohol test	X		X					X			
12-lead ECG [b]	X		X					X			
Vitals (BP, RR, HR, T) [c]	X	X	X		X	X	X	X	X	X	X
Chemistry, Hematology, Lipid Panel, and Urinalysis [e]	X		X		X	X		X		X	
Fasting (≥ 8-hr) plasma glucose [e]			X		X	X	X	X	X	X	X
Serum Ketones & Free Fatty Acids [e]			X		X	X	X	X	X	X	X
Study Drug SC Administration				X	X	X	X	X	X	X	X
Seven-point blood glucose profile [d]		X					X				X
Blinded Continuous Glucose Monitoring (CGM) [g]		X		X			X				X
Daily insulin usage dairy [h]		X	X	X	X	X	X				X
HbA1c	X		X						X		
Insulin, C-peptide, GLP-1, and Glucagon [e,]			X					X			
Serum PK sample collection [e]			X		X			X			
Anti-REMD-477 Ab sample collection [e]			X								
Exploratory biomarker collection [e]			X								
Liver Injury Biomarkers [e]			X					X			
Liver MRI/ FibroScan [j]			X								
QOL Questionnaires [i]			X								
Con-Med monitoring	X	←									→
Adverse event monitoring			←								→

Footnote Key:

a. Medical history includes significant past medical events (e.g. prior hospitalizations or surgeries), a review of diabetes history and glycemic control, and any concurrent medical illnesses.

b. After the Screening Visit, 12-lead ECG to be performed in triplicate, approximately 1 min apart. When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

c. Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.

d. Seven-point blood glucose profile will measure glucose by finger stick over three consecutive days before and 2 hours after each meal, and at bedtime.

e. Sample should be collected pre-dose on all dosing days.

f. FSH required at screening for post-menopausal women.

g. Blinded CGM will be performed for one week during the Lead-in Period (completed prior to the Baseline Visit), and for one week after Doses 1, 4, 8 and 12. CGM data will be downloaded at the clinical research unit during scheduled site visits, as indicated in the Schedule of Assessments.

h. Subjects will be given insulin usage diaries during the Lead-in Period and at the beginning of Weeks 1 through 4, 8, 12, 16, and 20. For one week of the Lead-in Period and Weeks 1 through 4, daily insulin use (short-acting, long-acting, and infusional as applicable) will be collected over seven days. For Weeks 8, 12, 16, and 20, daily insulin will be collected over a period of 3 consecutive days within that respective week.

i. The *WHO-5 Well-Being Index* & *T1-DDS* QOL Questionnaires will be completed by the subjects at the Baseline, Day 84, and Day 161.

j. Both the Liver MRI and FibroScan Baseline Assessments may be performed up to 7 days before the Day 1 Visit, after all other inclusion and exclusion criteria have been met.

Schedule of Assessments – Part B

Study Period (or Dose#)	Dose 9	Dose 10	Dose 11	Dose 12	Follow-up Period			EOS
Study Week	9	10	11	12	13	16	20	24
Study Day	57 ± 1	64 ± 1	71 ± 1	78 ± 1	85 ± 2	106 ± 2	134 ± 2	162 ± 2
Informed consent								
Medical History [a]								
Physical examination					X			X
Body weight	X				X	X	X	X
Urine pregnancy test (women); FSH [f]	X				X			X
Urine drug/alcohol test								X
12-lead ECG [b]	X		X		X			X
Vitals (BP, RR, HR, T) [c]	X	X	X	X	X	X	X	X
Chemistry, Hematology, Lipid Panel, and Urinalysis [e]	X				X			X
Fasting (≥ 8-hr) plasma glucose [e]	X	X	X	X	X			X
Serum Ketones & Free Fatty Acids [e]	X	X	X	X		X	X	
Study Drug SC Administration	X	X	X	X				
Seven-point blood glucose profile [d]				X		X	X	
Blinded Continuous Glucose Monitoring (CGM) [g]				X				
Daily insulin usage diary [h]				X		X	X	
HbA1c					X			X
Insulin, C-peptide, GLP-1, and Glucagon [e]	X				X	X		X
Serum PK sample collection [e]	X				X	X		
Anti-REMD-477 Ab sample collection [e]					X			X
Exploratory biomarker collection [e]					X			X
Liver Injury Biomarkers [e]	X				X	X		
Liver MRI/FibroScan [j]					X			
QOL Questionnaires [i]					X			X
Con-Med monitoring	◄							►
Adverse event monitoring	◄							►

Footnote Key:

a. Medical history includes significant past medical events (e.g. prior hospitalizations or surgeries), a review of diabetes history and glycemic control, and any concurrent medical illnesses.

b. After the Screening Visit, 12-lead ECG to be performed in triplicate, approximately 1 min apart. When ECG and blood sample collection occur at the same time, ECGs should be performed before blood samples are drawn.

c. Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.

d. Seven-point blood glucose profile will measure glucose by finger stick over three consecutive days before and 2 hours after each meal, and at bedtime.

e. Sample should be collected pre-dose on all dosing days.

f. FSH required at screening for post-menopausal women.

g. Blinded CGM will be performed for one week during the Lead-in Period (completed prior to the Baseline Visit), and for one week after Doses 1, 4, 8 and 12. CGM data will be downloaded at the clinical research unit during scheduled site visits, as indicated in the Schedule of Assessments.

h. Subjects will be given insulin usage diaries during the Lead-in Period and at the beginning of Weeks 1 through 4, 8, 12, 16, and 20. For one week of the Lead-in Period and Weeks 1 through 4, daily insulin use (short-acting, long-acting, and infusional as applicable) will be collected over seven days. For Weeks 8, 12, 16, and 20, daily insulin will be collected over a period of 3 consecutive days within that respective week.

i. The *WHO-5 Well-Being Index* & *T1-DDS* QOL Questionnaires will be completed by the subjects at the Baseline, Day 84, and Day 161.

j. Both the Liver MRI and FibroScan Baseline Assessments may be performed up to 7 days before the Day 1 Visit, after all other inclusion and exclusion criteria have been met.

Appendix B. Pharmacy Guide

REMD-477

Packaging and Formulation

REMD-477 will be manufactured and packaged by a certified CMO and distributed using a GCP-compliant clinical study drug distribution procedures. REMD-477 is supplied as single-use glass vials formulated with 10mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20 at a protein concentration of 70 mg/mL.

Placebo

Placebo will be presented in identical containers. The formulation of placebo is 10 mM sodium acetate, pH 5.2, 5% (w/v) sorbitol, 0.004% polysorbate 20

Labeling

Each single-use vial will list the study drug name, storage conditions, and the sponsor name. In compliance with regulations, it will also contain the statement, "New drug – Limited by Federal Law for Investigational Use."

Storage

The supplied REMD-477 must be stored at a temperature of –20°C or below and protected from light. Exposure of the material to temperatures outside these limits, except for warming prior to reconstitution and administration, may not occur and may result in the loss of activity. The clinical supplies must thaw overnight at 2 to 8°C in temperature-monitored refrigerators. Once thawed, vials should be transferred to room temperature and gently inverted to ensure mixing. Mixing may result in the formation of small bubbles, which is normal. Preparation of the clinical supplies should be performed using aseptic techniques and under sterile conditions.

All required drug preparation materials are listed at the end of this appendix with the catalog information.

Records of the actual storage conditions for REMD-477 during the period of the study must be maintained (e.g., records of the date and time and initials of person

checking, and the "working day" temperatures of the refrigerator used for storage of clinical study supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording). REMD Biotherapeutics must be notified if any investigational product is exposed to excessive or uncontrolled temperatures, in which case possible replacement of the material will be considered. Each vial is designated for single use only, and is not to be used to treat more than 1 subject. Vigorous shaking of the vials may denature the protein in solution and should be avoided.

Preparation

The exact preparation of the study drug will be described in detail in a separate document provided to the site in the Pharmacy Binder.

Supply and Return of Drug

At study initiation and as needed thereafter, investigational product will be shipped to a responsible person (e.g., a pharmacist) at the Principal Investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability Record. The Proof of Receipt Form should then be faxed to REMD Biotherapeutics and the original retained at the site. At the end of the study, or as directed, all investigational product supplies will be returned to REMD Biotherapeutics.

Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products mandated by the protocol must be kept current and should contain:

- the dates and quantities of investigational product received from REMD Biotherapeutics
- manufacturing lot number for investigational product received
- subject's identification (subject number and initials)
- date and quantity of investigational product dispensed
- the initials of the dispenser
- dose preparation records

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused investigational product to REMD Biotherapeutics. At the end of the study, the Final Investigational Product Reconciliation Statement must be completed and provided to REMD Biotherapeutics.

These inventories must be made available for inspection by an authorized REMD Biotherapeutics representative and regulatory agency inspectors. The Principal Investigator is responsible for the accountability of all used and unused clinical study supplies.

Appendix C. Insulin Infusion

INSULIN INFUSION TO OBTAIN **EUGLYCEMIA**

Written for insulin concentration of 100 units of regular insulin per 500ml of NS. Therefore all units/hr must be multiplied by 5 as below to get the correct ml/hr for the pump.

For Initiation, pump subjects start at ½ standard algorithm, nocturnal basal subjects start at ¼ standard, and AM basal insulin subjects start at 1/8 standard.

Below Goal Range **Less than 90 mg/dL**	***Within Goal Range*** **Less than 90 – 120 mg/dL**	***Above Goal Range*** **Over 120 mg/dL**
Less than 70 mg/dL • Turn off infusion • Follow Hypoglycemia orders • Recheck BG and re-retreat every 15. Then proceed according to the appropriate column of this table for next measured BG. **70 – 80 mg/dL** • Turn off infusion. • Check BG in 30 minutes. • Once BG is > 80mg/dl resume insulin infusion after moving one column to the **left**	**If BG decreased by 30 mg/dL between checks** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard, move **left** to ¼ Standard (Low) Algorithm and adjust rate per BG **If BG DECREASED by 1-30mg/dl or INCREASED by any amount** • Adjust rate in **current** algorithm per BG	**If BG decreased by more than 50 mg/dL** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard, move **left** to ¼ Standard (Low) Algorithm and adjust rate per BG. • Check BG in 15 minutes if decrease was over 100 mg/dL. **If BG decreased by 25 – 50 mg/dL** • Adjust rate in **current** algorithm per BG
80-90 mg/dL **If BG decreased by 30 mg/dL or more, or previous BG 80-90 mg/dL** • Move **left** one algorithm and adjust rate per BG. • If already at ½ Standard move **left** to ¼ Standard Algorithm and adjust rate per BG. • If already at ¼ algorithm, may remain there. **If BG decreased less than 30 mg/dL and/or previous BG was in goal range** • Adjust rate in **current** algorithm per BG.		**If BG increased by any amount, remained the same or decreased by less than 25 mg/dL** **Step 1.** Remain in **current** algorithm and adjust rate per BG. **Step 2.** If **after** remaining in **current** algorithm and next BG check continues to increase by any amount or decrease by less than 25 mg/dL, move **right** one algorithm **Step 3.** Check BG at the next time-point per protocol, and restart at step 1 if appropriate.

Insulin Infusion Algorithm

BG mg/dL	⅛ Standard units/hr (ml/hr)	¼ Standard units/hr (ml/hr)	½ Standard (Low) units/hr (ml/hr)	Algorithm 1 (Standard) units/hr (ml/hr)	Algorithm 2 units/hr (ml/hr)	Algorithm 3 units/hr (ml/hr)	Algorithm 4 units/hr (ml/hr)	Algorithm 5 units/hr (ml/hr)	Algorithm 6 units/hr (ml/hr)
80-90	0.1 (0.5ml/hr)	0.2 (1ml/hr)	0.3 (1.5ml/hr)	0.5 (2.5ml/hr)	0.6 (3ml/hr)	0.8 (4ml/hr)	1.0 (5ml/hr)	1.2 (6ml/hr)	1.4 (7ml/hr)
90 - 120	0.2 (1ml/hr)	0.3 (1.5ml/hr)	0.5 (2.5ml/hr)	0.7 (3.5ml/hr)	0.8 (4ml/hr)	1.0 (5ml/hr)	1.2 (6ml/hr)	1.4 (7ml/hr)	1.6 (8ml/hr)
121-160	0.3 (1.5ml/hr)	0.4 (2ml/hr)	0.7 (3.5ml/hr)	0.9 (4.5ml/hr)	1.1 (5.5ml/hr)	1.2 (6ml/hr)	1.4 (7ml/hr)	1.6 (8ml/hr)	1.8 (9ml/hr)
161-180	0.4 (2ml/hr)	0.5 (2.5ml/hr)	1 (5ml/hr)	1.1 (5.5ml/hr)	1.3 (6.5ml/hr)	1.5 (7.5ml/hr)	1.7 (8.5ml/hr)	1.9 (9.5ml/hr)	2.1 10.5ml/hr
181-220	0.5 (2.5ml/hr)	0.6 (3ml/hr)	1.2 (6ml/hr)	1.3 (6.5ml/hr)	1.5 (7.5ml/hr)	1.7 (8.5ml/hr)	1.9 (9.5ml/hr)	2.1 (10.5ml/hr	2.3 11.5ml/hr)
221-260	0.6 (3ml/hr)	0.8 (4ml/hr)	1.5 (7.5ml/hr)	1.7 (8.5ml/hr)	1.9 (9.5ml/hr)	2.1 (10.5ml/hr	2.3 (11.5ml/hr	2.5 (12.5ml/hr	2.7 (13.5ml/hr
261-300	0.8 (4ml/hr)	1 (5ml/hr)	2 (10ml/hr)	2.2 (11ml/hr)	2.4 (12ml/hr)	2.6 (13ml/hr)	2.8 (14ml/hr)	3.0 (15ml/hr)	3.2 (16ml/hr)
Over 300	1 (5ml/hr)	1.3 (6.5ml/hr)	2.5 (12.5ml/hr)	2.8 (14ml/hr)	3.0 (15ml/hr)	3.2 (16ml/hr)	3.4 (17ml/hr)	3.6 (18ml/hr)	4.0 (20ml/hr)

1. Monitor BG and adjust per algorithm above. Check BG every 30 minutes until it is within goal range of 90-120. BGs may then be checked every hour.

    a. BG target range: 90-120 mg/dL at all times
    b. Maintain blood glucose within range.
    c. If need to go above algorithm 6:
       Algorithm 7 = algorithm 6 + algorithm 1
       Algorithm 8 = algorithm 6 + algorithm 2 and so on
    d. The investigator (PI/SUB-I) may adjust insulin drip at their discretion if adjustments are deemed necessary outside of the algorithms.

***** In the event of hypoglycemia (BG < 70mg/dl)**

If BG < 50 mg/dL:
D/C INSULIN DRIP, Give 1 Amp (25 g) D50 IV; recheck BG q 15 minutes
⇒ When BG ≥ 100 mg/dL, wait 1 hour, then restart insulin drip at 50% of original rate

If BG 50-69 mg/dL:
D/C INSULIN DRIP If symptomatic (or unable to assess), give 1/2 Amp (12.5 g) D50 IV; recheck BG q 15 minutes
If asymptomatic, give 1/4 Amp (6.25 g) D50 IV OR 8 ounces Juice; recheck BG
⇒ When BG ≥ 100 mg/dL, wait 1 hour, then restart drip at 75% of original rate

Appendix D. Quality of Life Questionnaires

WHO-5 Well-Being Index

DIRECTIONS: Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks. Notice that higher numbers mean better well-being.
Example: If you have felt cheerful and in good spirits more than half of the time during the last two weeks, put a tick in the box with the number 3 in the upper right corner.

Over the last two weeks:	**All of the time**	**Most of the time**	**More than half of the time**	**Less than half of the time**	**Some of the time**	**At no time**
1. I have felt cheerful and in good spirits.	5	4	3	2	1	0
2. I have felt calm and relaxed.	5	4	3	2	1	0
3. I have felt active and vigorous.	5	4	3	2	1	0
4. I woke up feeling fresh and rested.	5	4	3	2	1	0
5. My daily life has been filled with things that interest me.	5	4	3	2	1	0

T1-DDS

Instructions

Living with type 1 diabetes can be tough. Listed below are a variety of distressing things that many people with type 1 diabetes experience. Thinking back **over the past month**, please indicate the degree to which each of the following may have been a problem for you by circling the appropriate number. For example, if you feel that a particular item was not a problem for you over the past month, you would circle "1". If it was very tough for you over the past month, you might circle "6".

		Not a problem	A slight problem	A moderate problem	A somewhat serious problem	A serious problem	A very serious problem
1	Feeling that I am not as skilled at managing diabetes as I should be.	1	2	3	4	5	6
2	Feeling that I don't eat as carefully as I probably should.	1	2	3	4	5	6
3	Feeling that I don't notice the warning signs of hypoglycemia as well as I used to.	1	2	3	4	5	6
4	Feeling that people treat me differently when they find out I have diabetes.	1	2	3	4	5	6
5	Feeling discouraged when I see high blood glucose numbers that I can't explain.	1	2	3	4	5	6
6	Feeling that my family and friends make a bigger deal out of diabetes than they should.	1	2	3	4	5	6
7	Feeling that I can't tell my diabetes doctor what is really on my mind.	1	2	3	4	5	6
8	Feeling that I am not taking as much insulin as I should.	1	2	3	4	5	6
9	Feeling that there is too much diabetes equipment and stuff I must always have with me.	1	2	3	4	5	6
10	Feeling like I have to hide my diabetes from other people.	1	2	3	4	5	6
11	Feeling that my friends and family worry more about hypoglycemia than I want them to.	1	2	3	4	5	6
12	Feeling that I don't check my blood glucose level as often as I probably should.	1	2	3	4	5	6
13	Feeling worried that I will develop serious long-term complications, no matter how hard I try.	1	2	3	4	5	6

		Not a problem	A slight problem	A moderate problem	A somewhat serious problem	A serious problem	A very serious problem
14	Feeling that I don't get help I really need from my diabetes doctor about managing diabetes.	1	2	3	4	5	6
15	Feeling frightened that I could have a serious hypoglycemic event when I'm asleep.	1	2	3	4	5	6
16	Feeling that thoughts about food and eating control my life.	1	2	3	4	5	6
17	Feeling that my friends or family treat me as if I were more fragile or sicker than I really am.	1	2	3	4	5	6
18	Feeling that my diabetes doctor doesn't really understand what it's like to have diabetes.	1	2	3	4	5	6
19	Feeling concerned that diabetes may make me less attractive to employers.	1	2	3	4	5	6
20	Feeling that my friends or family act like "diabetes police" (bother me too much).	1	2	3	4	5	6
21	Feeling that I've got to be perfect with my diabetes management.	1	2	3	4	5	6
22	Feeling frightened that I could have a serious hypoglycemic event while driving.	1	2	3	4	5	6
23	Feeling that my eating is out of control.	1	2	3	4	5	6
24	Feeling that people will think less of me if they knew I had diabetes.	1	2	3	4	5	6
25	Feeling that no matter how hard I try with my diabetes, it will never be good enough.	1	2	3	4	5	6
26	Feeling that my diabetes doctor doesn't know enough about diabetes and diabetes care.	1	2	3	4	5	6
27	Feeling that I can't ever be safe from the possibility of a serious hypoglycemic event.	1	2	3	4	5	6
28	Feeling that I don't give my diabetes as much attention as I probably should.	1	2	3	4	5	6