Official Protocol Title:	A Study to Assess the Safety, Pharmacokinetics and Pharmacodynamic Effect of MK-5160 in Subjects with Type 1 and Type 2 Diabetes Mellitus
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TITLE:

A Study to Assess the Safety, Pharmacokinetics and Pharmacodynamic Effect of MK-5160 in Subjects with Type 1 and Type 2 Diabetes Mellitus

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 TRIAL SUMMARY

Abbreviated Title	Multiple ascending dose study of MK-5160 in subjects with Type 1 and Type 2 diabetes mellitus
Sponsor Product Identifiers	MK-5160
Trial Phase	Phase 1
Clinical Indication	Diabetes mellitus
Trial Type	Interventional
Type of control	Placebo and active control without placebo
Route of administration	Subcutaneous
Trial Blinding	Double-blind
Treatment Groups	Part 1 (T1DM): MK-5160 16 nmol/kg or glargine 0.4 U/kg MK-5160 32 nmol/kg or glargine 0.4 U/kg MK-5160 </= 64 nmol/kg or glargine 0.4 U/kg Part 2 (T2DM): MK-5160 16 nmol/kg or glargine 0.6 U/kg MK-5160 32 nmol/kg or glargine 0.6 U/kg MK-5160 </= 64 nmol/kg or glargine 0.6 U/kg
Number of trial subjects	Approximately 48 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 8 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 6-8 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a washout phase of 4 days each subject will be receiving assigned treatment for approximately 2 weeks. After the end of treatment each subject will be followed for 19 days.
Randomization Ratio	3:1 (MK-5160/glargine)

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, active- and placebo-controlled, parallel-group, single-site, double-blind trial of MK-5160 in subjects with type 1 and type 2 diabetes mellitus (DM).

This is a two-part trial, with three panels per part. Type 1 diabetes mellitus (Part 1) and Type 2 DM (Part 2) subjects will be given daily fixed doses of MK-5160 or glargine (active comparator) in three predefined, increasing doses in each panel. The first panel in Part 1 will be the initial panel; the second panel in Part 1 and first panel in Part 2 will be initiated after review of preliminary safety and pharmacodynamics from the initial panel. Different subjects will participate in each panel.

T2DM subjects in Part 2 may be on a single anti-hyperglycemic agent (AHA) of a permissible class (metformin, DPP4 inhibitor, sulfonylurea, or alpha-glucosidase inhibitors) **or** metformin in combination with one additional permissible AHA (a DPP4 inhibitor, sulfonylurea, or alpha-glucosidase inhibitor), at stable doses for at least 8 weeks prior to screening. Subjects may also be on insulin in addition to the above, or on insulin alone.

Subjects taking metformin and/or a DPP-4 inhibitor will continue these medications at their pre-enrollment doses throughout study participation, but subjects taking a sulfonylurea or an alpha-glucosidase inhibitor will discontinue the sulfonylurea or alpha-glucosidase inhibitor at screening, at least 7 days prior to CRU admission, and remain off until the completion of dosing.

All subjects would be brought into the site on Day -4, placed on continuous glucose monitoring (CGM), and started on an appropriate dose of fast-acting insulin, to be administered via a subcutaneous (SC) pump that will remain in place for the duration of dosing. The SC pump will be placed in all subjects during the washout period with the exception of non-insulin requiring T2DM subjects. Subjects will be domiciled for the entirety of MK-5160/glargine dosing, receiving standard meals and snacks. Prandial and (if needed) rescue insulin will be dosed throughout the trial according to standard clinical practice and at the discretion of the investigator, taking both the pre-prandial glucose level (fingerstick) and the carbohydrate content of the planned meal into account. In addition, subjects will have fingerstick glucose levels checked prior to bedtime and once overnight, and as needed per the subject and/or Investigator.

On Day -1, the insulin via the SC pump will be discontinued, and subjects will be fasted overnight while also receiving insulin and dextrose via IV infusions, as needed, to set plasma glucose levels at 100 mg/dL prior to dosing and clamp initiation. On Day 1, subjects will be administered MK-5160 or glargine (3:1) SC. Subjects will be blinded in a double-dummy fashion, so that each subject will get two injections, one of which would be placebo. Subjects would continue to be on CGM, but will also be on a euglycemic clamp (fasted) for ~24 hours after this first dose. After completion of the euglycemic clamp, subjects will restart the standardized diet and continue to receive daily SC MK-5160/glargine at the same dose, with continued prandial insulin at the dosing discretion of the investigator via the SC pump. If necessary to treat hyperglycemia, subjects may also receive bolus and/or infused insulin via the SC pump, at the discretion of the Investigator.

On Day 7, subjects will not be given an evening meal or a pre-bedtime snack, while continuing to be domiciled and on CGM. A "pre-dinner" glucose measurement will be obtained, and hyperglycemia will be corrected if necessary, but subjects will then initiate a fast. By not taking the evening meal and snack on Day 7, subjects will be exposed to a fasting stress to assess the extent of nighttime hypoglycemia, while the subjects continue to be closely monitored. Hypoglycemia (and hyperglycemia), if observed, will be treated as outlined in Appendix 12.6, at the discretion of the Investigator according to the site's standard operating procedures. If the individual subject does not require intervention for hypoglycemia after this Day 7 fast, a similar fasting will occur for that subject on Day 9. Subjects will have a normal meal schedule on Day 8, and on Days 10-11.

MK-5160 is expected to be at steady-state prior to Day 12. On the evening of Day 11, subjects will be fasted overnight on insulin and dextrose IV infusions, and then given MK-5160/glargine on a euglycemic clamp, as on Day 1. This clamp may continue beyond 24 hours, to assess duration of action. After completion of this clamp, subjects will restart the standardized diet but also restart their home insulin regimen. Subjects will be discharged from site ~48 hours after the final clamp, when glucose levels are stable.

In addition to the extensive glucose monitoring (CGM, euglycemic clamp, pre-prandial and overnight assessment), subjects will be evaluated for the effects of MK-5160/glargine on lipid metabolism and ketogenesis. Fasting plasma levels of free fatty acids (FFA, also known as NEFA), glycerol, and triglycerides, as well as beta-hydroxybutyric acids (BHA) will be collected throughout the trial.

Subjects will have intense pharmacokinetic (PK) sampling during the clamps, with daily sampling at other times during dosing and up to one week after dosing. Vital signs and ECGs will be collected at specified times throughout the trial, especially during anticipated steady state of MK-5160. Safety laboratory studies will be obtained predose, after the first dose (during the clamp), at steady state and after completion of the dosing. Anti-drug antibodies (ADA) will also be collected pre-dose and after completion of treatment.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Because this is a Phase I assessment of MK-5160 in humans, the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being elucidated. This protocol is therefore written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Please refer to Section 7.1.5 – Visit Requirements for examples of modifications permitted within the protocol parameters.

2.2 Trial Diagram

The trial/study design is depicted in Figure 1, Figure 2 and Table 1.

Part 1 will start first, and initiation of Part 2 will occur after review of preliminary safety and pharmacodynamic results from the first panel in Part 1. Subjects will participate in only one panel. Subjects will get injections of MK-5160/glargine and placebo matched to the alternative active treatment.

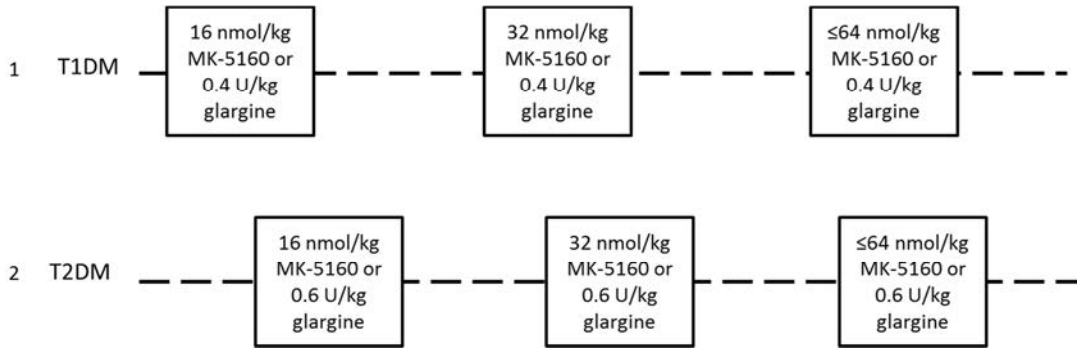

Figure 1 Overall Trial Design

The general overall plan is depicted. After admission to the CRU, subjects will discontinue their home diabetes regimen (including insulin) and be placed on continuous glucose monitoring (CGM) and a SC insulin pump to control glucose (if needed). On Day -1, this will be converted to IV infusions of insulin and dextrose to set plasma glucose for dosing and first clamp on Day 1. After 24 hours, the clamp will be discontinued and subjects will resume a normal diet on MK5160/glargine. On Days 7 and 9, subjects will be partially fasted. On Day 12, subjects will undergo a second clamp for up to 30 hours, and restart their home regimen. Subjects will continue to be domiciled and observed on the home regimen, with continued pharmacokinetic assessment.

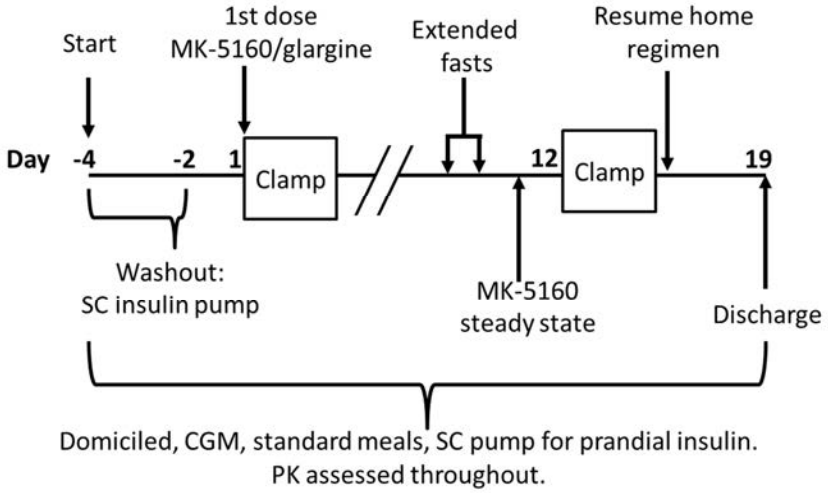

Figure 2 Study Design

Table 1 Trial Design

Part 1 (T1DM)	Panel A[a]	Panel B	Panel C
	MK-5160 16 nmol/kg or glargine 0.4 U/kg	MK-5160 32 nmol/kg[b] or glargine 0.4 U/kg[c]	MK-5160 ≤64 nmol/kg[b] or glargine 0.4 U/kg[c]
Part 2 (T2DM)	Panel D	Panel E	Panel F
	MK-5160 16 nmol/kg[b] or glargine 0.6 U/kg[c]	MK-5160 32 nmol/kg[b] or glargine 0.6 U/kg[c]	MK-5160 ≤64 nmol/kg[b] or glargine 0.6 U/kg[c]

[a] Within each treatment panel, 6 subjects will be randomized to receive MK-5160 and 2 subjects to receive glargine according to a computer-generated allocation schedule. In addition to MK-5160 or glargine, subjects will also receive placebo (i.e., subjects receiving MK-5160 will also receive placebo matched to glargine, and subjects receiving glargine will also receive placebo matched to MK-5160).

[b] The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous treatment periods.

[c] The suggested glargine doses may be adjusted downward or upward, based on evaluation of pharmacodynamics data observed in previous treatment periods

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the safety of multiple SC doses of MK-5160 in adult subjects with T1 and T2 DM.
2) **Objective:** To determine the maximal glucose infusion rate required to maintain target glucose levels in a euglycemic clamp setting (GIR_{max}) of MK-5160 in adult subjects with T1 and T2 DM at steady-state following SC dosing.

   Hypothesis: At a dose with sufficient safety, the mean steady-state maximum level of GIR (GIRmax) after MK-5160 administration in both T1 and T2 DM patients is between 1.5 and 4.5 mg/kg/min.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To estimate the plasma PK profile (e.g. Cmax, Css, Steady State AUC0-24hr, CL, Tmax) of MK-5160 after SC administration.

3.3 Exploratory Objectives

1) **Objective:** To explore the levels of plasma triglycerides (TG), FFA and glycerol after SC doses of MK-5160 compared to glargine, in order to assess the effect of MK-5160 on lipolysis.
2) **Objective:** To explore the effect of MK-5160 on fasting morning glucose after SC doses of MK-5160 compared to glargine, as a secondary analysis for the effect of MK-5160 on glucose metabolism.
3) **Objective:** To assess the relationship between PK parameter values of MK-5160 with BMI after SC administration.
4) **Objective:** To explore the incidence and nature of nighttime and other episodes of potential hypoglycemia, using fingerstick glucose levels and CGM data.
5) **Objective:** To explore possible changes in counterregulatory hormones (e.g., glucagon) after treatment with MK-5160.
6) **Objective:** To explore the relationship between exposure and subdivisions of GIR (i.e., GIR AUC0-24, AUC0-12, AUC12-24, AUC24-end of clamp [for final clamp]) after one dose and at steady state.
7) **Objective:** To explore the relationship between daily non-basal insulin requirements (prandial and any corrective doses given) in MK-5160 vs. glargine treatment.
8) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-5160.

4.1.1 Pharmaceutical and Therapeutic Background

Diabetes mellitus (Type 1 and Type 2; T1DM, T2DM) is a global public health issue believed to affect over 400 million individuals worldwide in 2015, and is estimated to affect almost 650 million by 2040. Currently nearly 10% of the U.S. population is directly affected by the disease, and by 2050 it is estimated that 1 in 3 American adults will have diabetes. According to CDC statistics, 14% of all diabetics in the U.S. are on insulin alone, and another 13% are on a combination of insulin and oral therapy. All insulin-treated patients utilize basal insulin, which is intended to maintain normal plasma glucose levels during fasting.

Although insulin has been a mainstay of diabetes therapy for decades, exogenously administered insulin poses short-term risks and long-term drawbacks. Excessive basal insulin leads to hypoglycemia, followed by several days of dose adjustment to achieve a new steady-state response. Practitioners and patients often settle at moderate under-dosing of basal insulin, mitigating the risk for hypoglycemia at the expense of not achieving target glycemic levels and thereby increasing the risk of long term complications of diabetes.

The goal of the Insulin Receptor Partial Agonist (IRPA) program is to develop a novel, once-daily SC basal insulin with a wide therapeutic index (TI), permitting more aggressive treatment to the glycemic target with reduced risk of hypoglycemia. The improved TI of an IRPA would significantly reduce the risk of hypoglycemia relative to available therapies, thus allowing more confidence for practitioners and patients to dose-titrate IRPA to attain target goals for control of fasting glucose. An IRPA is expected to have hepato-adipose preferentiality as a result of greater activation of insulin receptors in those tissues relative to skeletal muscle.

[redacted]

A generally accepted surrogate for measurement of the physiologic response to insulin with respect to glucose lowering is the euglycemic clamp procedure, in which subjects are given a fixed dose of insulin, and plasma glucose levels are set to a target level using a variable glucose infusion. Several previous studies have demonstrated that inhibition of hepatic glucose production corresponds to a glucose infusion rate (GIR) of 1.5-2.0 mg/kg/min in the euglycemic clamp. Inhibition of lipolysis at doses leading to GIRs in this range would support a hepato-adipose preferential activity.

4.1.2 Ongoing Clinical Trials

MK-5160-001 (P001) is an active-controlled and placebo-controlled, single-site, three-part trial of MK-5160 in healthy adult subjects which is completed with ongoing data assessment. P001 is being conducted to assess the initial clinical safety, tolerability, PK and pharmacodynamics (PD) of MK-5160 following administration to humans. PK after both IV and SC administration is being assessed. PD is being assessed by evaluating the glucose infusion rate (GIR) after administration of MK-5160 under euglycemic clamp conditions, and by assessing plasma free fatty acid (FFA) and glycerol levels. In addition, the potential antagonistic effect of MK-5160 on rapid-acting insulin is being assessed, also under euglycemic clamp conditions.

To date a total of 88 subjects have been enrolled. Approximately 63 subjects have been dosed with MK-5160, which has been generally well tolerated. Adverse events (AEs), vital signs, exams, ECGs and laboratory safety studies have been generally unremarkable. [redacted]

These results support hepato-adipose preferential activity of MK-5160, which further supports testing of MK-5160 as a novel basal insulin in T1 and T2DM patients.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study is being conducted to assess the safety, tolerability, PK and PD of MK-5160 following administration to patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). PK in both T1DM and T2DM subjects will be assessed. PD, as GIR, will be assessed using a euglycemic clamp in T1DM and T2DM subjects after the first dose and at steady-state after SC dosing of MK-5160. In addition, plasma FFA and glycerol levels will be assessed to understand PD with respect to lipolysis.

The acceptable GIRmax is derived from the target GIRmax of 1.5-2.0 mg/kg/min, which reflects inhibition of hepatic glucose production, with the upper limit (4.5 mg/kg/min) reflecting the maximum observed GIR in studies of the hepato-preferential peglispro. PD will also be assessed by examining fasting morning glucose levels after administration of standard of care (SOC) or MK-5160, and other PD endpoints will include variability of glucose levels, as determined by CGM, and inhibition of lipolysis.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for The Use of Comparator/Placebo

Glargine (U100) will be administered as a comparator for MK-5160. Subjects will be randomized to receive glargine or MK-5160 in both parts. The use of glargine is to confirm the PD profile of glargine compared to MK-5160 in this population, and to serve as a safety comparator for MK-5160. PD will be assessed as the GIR required to maintain the prespecified euglycemic clamp (100 mg/dL). In addition to PD, glargine will be used as a comparator for safety – for AEs and for laboratory and other safety markers – against MK-5160.

Glargine will be administered at a dose of 0.4 U/kg in Part 1 (T1DM subjects), as this dose leads to a GIR of ~1.5 mg/kg/min in a euglycemic clamp study of T1DM subjects [1]. To account for insulin resistance in the T2DM population, the dose in Part 2 will be 0.6 U/kg.

To facilitate blinding, each subject will get two injections at each administration timepoint. Subjects will be dosed with MK-5160 and placebo matched with glargine, or glargine and placebo matched to MK-5160.

4.2.2.2 Starting Dose for This Trial

In the diabetic patient populations to be studied in this trial, the lowest dose of MK-5160 should be an effective dose to reduce the likelihood of hyperglycemia and its associated complications. Note that all patients will be domiciled and closely monitored throughout the trial, and that T1DM patients will also be receiving prandial insulin reflective of intake and pre-prandial plasma glucose, in accordance with standard clinical practice. This will reduce the likelihood of hyperglycemia. In addition, the Investigator has discretion to administer corrective fast-acting insulin via the SC pump, either as a bolus or as an infusion.

The proposed starting dose of MK-5160 in this trial is 16.0 nmol/kg SC daily for 12 days, in both the T1DM and T2DM parts. [redacted]

[redacted]

The projected steady-state AUC0-24hr for a daily dose of 16 nmol/kg is 31 nM*hr. [redacted] Thus, the NOAEL was set at the dog exposure of 814 nM*hr, which sets a margin of 26x for this initial dose of 16 nmol/kg SC. [redacted]

The expected accumulation of MK-5160 after SC administration is such that the steady state AUC0-24hr of 31 nM*hr is expected to be reached ~ 7 days. [redacted]

The first panel of Part 1 (T1DM) will be dosed initially. Dosing for the first panel of Part 2 will commence after at least four subjects have completed dosing, and a review of available preliminary safety data and initial pharmacodynamic data is completed. The decision to initiate Part 2 and proceed in Part 1 will be made by both the Investigator and Sponsor, after review of the available data, and will be communicated via a letter to the investigator.

4.2.2.3 Maximum Dose/Exposure for This Trial

[redacted] Subjects in this trial will be domiciled and closely monitored. Moreover, the overall intent of this trial is to maintain plasma glucose levels in the normal physiologic range. As directed by the CTA Guidance [ICH Topic M3 (R2)], the maximum allowable exposure in this trial is the lower exposure (AUC) in either species at the highest dose tested, as neither species demonstrated toxicity not related to the pharmacological activity of MK-5160, and at least 3 dose levels were assessed in both.

The projected dose range for MK-5160 after daily SC administration has been estimated, based on P001, preclinical studies and extensive modeling. The maximum proposed dose in both T1DM and T2DM subjects is 64 nmol/kg SC daily, which is projected to lead to a steady state exposure (AUC0-24hr) of 124 nM*hr. [redacted]

[redacted]

An anticipated insulin resistance of ~1.5-2x in T2DM subjects would lead to an equivalent effect of ~½ of the above nM*hr in healthy subjects or T1DM subjects, which is equivalent to the insulin to be delivered at 32 nmol/kg in those subjects. [redacted] The top dose in the trial may be decreased if results from the first two panels show satisfactory GIR and glucose lowering.

[redacted] Subjects in this trial will be receiving a glucose infusion via the euglycemic clamp on Day 1 and at steady state, and will be closely observed and frequently monitored for the duration of dosing and after discontinuation of the steady-state clamp.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

As this is an early clinical investigation of MK-5160, safety will be carefully monitored. Physical examinations, vital signs, 12-lead electrocardiograms (ECG), laboratory safety tests (serum chemistry, hematology, and urinalysis) and monitoring of adverse experiences (AEs) will be assessed throughout the dosing intervals, with assessment collection times optimized based on the expected PK properties of MK-5160. [redacted]. Specific restrictions are set forth in the inclusion and exclusion criteria regarding blood pressure, potassium levels, magnesium levels, and ECG findings, where only normal findings are acceptable for inclusion of subjects (see Section 5, Methodology, for details). Additional monitoring of potassium levels at the bedside may be performed at the discretion of the investigator. Additionally, due to the fluid load required for a clamp procedure, normal blood pressure and renal function will be required from a safety standpoint. Vital signs and ECG readings will be performed throughout the study to monitor any potential untoward effects (see Section 6.0, Trial Flow Chart, for details). Subject discontinuation criteria for QTc abnormalities have been defined (see Section 5.8 and 12.4 for details). Standard chemistry, hematology and urinalysis panels will be assessed along with careful and frequent glucose monitoring.

MK-5160 administration could lead to anti-drug antibody (ADA) formation. [redacted] ADA and AIA will be assessed pre-dose and at 14 and 28 days post dose (see section 7.1.5.3.

for post-trial follow-up). Drug-induced positive ADA and AIA will be further evaluated for neutralizing activity.

4.2.3.2 Pharmacokinetic Endpoints

The PD endpoint will be coupled with plasma MK-5160 concentration, to help assess the time-action profile for SC administration of MK-5160. In addition, C_{max} and T_{max}, plasma exposures (AUC_{0-24hr}) and additional plasma concentration parameters (C_{24hr}) will also be measured, as will apparent terminal half-life ($t_{1/2}$) reflective of the absorption half-life after SC administration.

4.2.3.3 Pharmacodynamic Endpoints

The primary objective in this study, in addition to evaluation of safety, is to gain an understanding of the pharmacodynamic effect of MK-5160, as this will predict the ability of MK-5160 to function as a hepato-adipose selective basal insulin. Evaluation of glucose lowering, as GIR in the euglycemic clamp and as measurements in continuous glucose monitoring, in addition to evaluation of lipolysis will be key to understanding MK-5160.

Evaluation under euglycemic clamp conditions protects subjects from hypoglycemia, and allows a quantitative and comparable determination of PD. At euglycemia, full agonist insulins such as RHI require a maximum GIR of approximately 10-11 mg/kg/min to prevent hypoglycemia, reflecting a combination of suppressed hepatic glucose production and insulin-mediated glucose disposal, primarily into muscle. [redacted] Previous studies have demonstrated that hepatic glucose production corresponds to a GIR of 1-2 mg/kg/min, while activation of muscle glucose uptake corresponds with GIRs of greater than 4 mg/kg/min [5,6]. GIRs between 2 and 4 mg/kg/min are attributed to inhibition of hepatic glucose uptake, in addition to changes in tissue-specific glucose utilization. Of note, the hepatoselective insulin peglispro leads to a maximum GIR of ~4 mg/kg/min [7] which included a mild effect on presumed muscle uptake. Thus, MK-5160 GIR should predict tissue selectivity, and in the proposed trial a hepatopreferential activity can be evaluated in T1 and T2DM patients.

In general, the concentration of insulin is thought to be the primary driver for GIR in the euglycemic clamp. As an exploratory analysis, the relationship between exposure, as well as subdivisions of exposure (AUC0-24, AUC0-12, AUC12-24), with GIR will be examined.

Evaluation of the ability of MK-5160 to inhibit lipolysis will be critical, as the results of peglispro trials suggest that the hepatic effects of insulin alone result in accumulation of liver triglyceride and elevated aminotransferases. [redacted] fasting plasma FFA (non-esterfied fatty acids - NEFA) and glycerol will be evaluated in this trial to assess the effect of MK-5160 on lipolysis, and in this trial serum triglycerides will also be assessed, as an effect on triglycerides may be more apparent after the extended dosing.

Inhibition of ketogenesis is an additional important desirable effect of an ideal basal insulin, and as this is almost exclusively a hepatic process, it would be expected that MK-5160 would inhibit ketogenesis. [redacted]

cci [redacted] To assess ketosis, β-hydroxybutyrate will be assessed.

NEFA, glycerol, and β-hydroxybutyrate will be correlated with MK-5160 PK and glucose PD to more fully understand the complete PD profile for MK-5160.

GIR will be adjusted to maintain plasma glucose levels 100 mg/dL. After and during the dosing of MK-5160 or glargine, glucose levels will be monitored at the bedside and the GIR will be adjusted accordingly. To address the primary hypothesis around GIR, the values of interest are the individual maximal GIR (GIRmax) values at steady state, which is anticipated to fall between 1.0-2.0 mg/kg/min cci [redacted]. As detailed below (Section 8), the GIRmax values at steady state will comprise the analysis. Within each panel, glargine will be given to two of the subjects who have been randomized along with the six subjects being given MK-5160.

In addition to the key endpoints noted above, additional exploratory endpoints will be examined to achieve a richer understanding of the actions of MK-5160 in diabetic patients. Along with the analysis of GIR noted above, data on morning fasting glucose will be collected, as will extensive data on glucose levels using CGM. These data will be closely examined during the longer fasting periods during the trial, to explore the degree to which plasma glucose levels fall during prolonged fasting while subjects are on MK-5160 or glargine. This will aid in understanding the potential risk of MK-5160 to lead to hypoglycemia. As noted, the subjects will be carefully monitored for symptomatic hypoglycemia and for glucose levels requiring intervention.

MK-5160 will be administered to T2DM patients, who generally are overweight to obese and thus have increased subcutaneous tissue that may complicate absorption and thus lead to variability in PK. It is anticipated that the T2DM subjects enrolled in this trial will cover a range of BMI, and thus PK with respect to BMI will be examined.

Additional exploratory analysis includes an examination of the effects of MK-5160 and glargine on counterregulatory hormones – specifically, glucagon. Hypoglycemia results in elevation of glucagon levels in non-diabetic patients, but this response is often blunted or absent in T1DM patients (and some T2DM patients), likely due to the action of insulin on glucagon-secreting alpha cells. MK-5160 may not have this effect on alpha cells, due to the tissue selectivity, and thus plasma glucagon levels will be measured when plasma glucose levels are expected to be low.

4.2.3.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response and the molecular basis of disease is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation and/or disease. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. Knowledge of the molecular basis of disease contributes to the development of novel biomarkers and the identification of new drug targets. This research contributes to understanding molecular basis

of disease and the genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with T1DM or T2DM between the ages of 18 and 60 or 65 years (inclusive, respectively) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

For Part 1 (T1DM):

1. Subjects provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be male, or female of non-childbearing potential between 18 to 60 years of age at the pre-trial (screening) visit.

   A female of non-childbearing potential is defined as:

   a. A female who is postmenopausal without menses for at least 1 year and has a follicle stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,

   b. A female who is status post hysterectomy, oophorectomy or tubal ligation.

      i. NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents

3. Be judged to be in good health based on medical history, physical examination, vital sign measurements, ECG, and laboratory safety tests (Section 7.1.3.1) performed at pretrial (screening) and prior to administration of the initial dose of trial drug. Appendix 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria and Appendix 12.5 provides an algorithm for the assessment of out-of-range laboratory values. Subjects with the following conditions may be enrolled:

   a. Hypertension treated with lifestyle modification alone or stable doses (no change for ≥3 months) of ≤2 antihypertensive agents of the following drug classes: angiotensin converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers, and diuretics (chlorthalidone or a thiazide diuretic. Loop diuretics and beta-blockers are NOT permitted).

   b. Non-proliferative diabetic retinopathy, if subject is under the regular care of an ophthalmologist and is up-to-date and compliant with the prescribed ongoing evaluation and management. Subjects with other diagnosed complications of diabetes, such as peripheral neuropathy and microalbuminuria, may also be included.

   c. Subjects without history of myocardial infarction (MI) but who are on aspirin may be enrolled. Subjects with a history of MI or atherosclerosis are not eligible.

   d. Other conditions, such as gastroesophageal reflux disease, obstructive sleep apnea, osteoarthritis, psoriasis, mood disorders and other chronic stable conditions may be allowed, at the discretion of the Investigator and Sponsor.

4. Have a diagnosis of T1DM as defined by standard diagnostic criteria for ≥12 months at time of screening.

5. Have a serum C-peptide concentration ≤0.7 ng/mL (0.23 nM) with a concurrent plasma glucose >90 mg/dL (5 mM).

6. Be on stable doses of basal insulin over the 2-week period prior to screening and over the 2 weeks prior to dosing. Stability is defined as within approximately ±20% difference in total daily insulin doses. Insulin pump users will be allowed.
7. Have a total daily insulin requirement (basal plus prandial) of ≤ 1.2 units/kg.
8. Have a HbA1c ≤10% at the screening visit.
9. Have a Body Mass Index (BMI) ≥18.5 kg/m2 and ≤ 32 kg/m2. BMI = mass (kg)/height (m)2
10. Be a non-smoker or smoker who uses no more than 5 cigarettes or equivalent (e.g., e-cigarettes) per day over the prior 3 month period also may be enrolled (at the discretion of the investigator). The subject must agree to follow the smoking restrictions defined by the CRU.
11. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

For Part 2 (T2DM):

1. Subjects provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be male, or female of non-childbearing potential between 18 to 65 years of age at the pre-trial (screening) visit.

   A female of non-childbearing potential is defined as:

   a. A female who is postmenopausal without menses for at least 1 year and has a follicle stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,

   b. A female who is status post hysterectomy, oophorectomy or tubal ligation.

      i. NOTE: These procedures must be confirmed with medical records. In the absence of documentation, hysterectomy may be confirmed by pelvic exam or if necessary by ultrasound; oophorectomy may be confirmed by hormone levels, particularly FSH in the post-menopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents

3. Be judged to be in good health based on medical history, physical examination, vital sign measurements, ECG, and laboratory safety tests (Section 7.1.3.1) performed at pretrial (screening) and prior to administration of the initial dose of trial drug . Appendix 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria and Appendix 12.5 provides an algorithm for the assessment of out-of-range laboratory values. Subjects with the following conditions may be enrolled:
    a. Hypertension treated with lifestyle modification alone or stable doses (no change for ≥3 months) of ≤2 antihypertensive agents of the following drug classes: angiotensinconverting enzyme inhibitors (ACE-inhibitors), angiotensin receptor blockers (ARBs), calcium channel blockers, and diuretics (chlorthalidone or a thiazide diuretic. Loop diuretics and beta-blockers are NOT permitted).
    b. Hypercholesterolemia with stable doses of treatment (no change for ≥ 3 months), including HMG-CoA reductase inhibitors (statins). Subjects on alternative medications for hypercholesterolemia may be allowed, at the discretion of the Investigator and the Sponsor.
    c. Subjects without history of myocardial infarction (MI) but who are on aspirin may be enrolled. Subjects with a history of MI or atherosclerosis are not eligible.
    d. Non-proliferative diabetic retinopathy, if subject is under the regular care of an ophthalmologist and is up-to-date and compliant with the prescribed ongoing evaluation and management. Subjects with other diagnosed complications of diabetes, such as peripheral neuropathy and microalbuminuria, may also be included.
    e. Other conditions, such as gastroesophageal reflux disease, obstructive sleep apnea, osteoarthritis, psoriasis, mood disorders and other chronic stable conditions may be allowed, at the discretion of the Investigator and Sponsor.
4. Have a diagnosis of T2DM as defined by standard diagnostic criteria for ≥12 months at time of screening.
5. T2DM subjects are not required to have been on insulin. If on insulin, subjects should have a total daily insulin requirement of ≤ 1.2 units/kg, and have been on stable doses of basal insulin over the 2-week period prior to screening and over the 2 weeks prior to dosing. Stability is defined as within approximately ±20% difference in total daily insulin doses.
6. In addition to the insulin criteria in #5, meet one of the following criteria:
    a. Be on no AHA, or on metformin monotherapy or metformin plus a DPP4 inhibitor at stable doses for at least 8 weeks prior to screening, with a screening HbA1C ≥7.0 and ≤10.0%.

b. Be on either a sulfonylurea (e.g. glyburide) or an alpha-glucosidase inhibitors (e.g., acarbose) alone or in combination with metformin at stable doses for at least 8 weeks prior to screening with a screening HbA1C ≥7.0 and ≤9.0%. Subjects on these medications must be willing to stop the sulfonylurea or alpha-glucosidase inhibitor after screening once they qualify for study participation.

7. Have a BMI ≥18.5 kg/m^2 and ≤ 35.0 kg/m^2 BMI = mass (kg)/height $(m)^2$
8. May be on selected standard medications for T2DM, including alpha-glucosidase inhibitors (e.g., acarbose), sulfonylureas (e.g. glyburide), DPP-4 inhibitors, and metformin. Subjects on alpha-glucosidase inhibitors and/or sulfonylureas must stop these medications for at least one week prior to checking into the site and for the duration of the trial through the last dose of MK-5160/glargine. Subjects on metformin or DPP-4 inhibitors may continue on their home dose for the duration of the trial. Subjects on SGLT2 inhibitors (gliflozins), thiazolidinediones or GLP-1 agonists are excluded.
9. Be a nonsmoker or smoker who uses no greater than 5 cigarettes or equivalent (e.g., e-cigarettes) daily over the prior 3 month period. Subjects must agree to follow the smoking restrictions defined by the CRU.
10. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

For Part 1 (T1DM):

1. Is under the age of legal consent

2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine (excluding diabetes mellitus), gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator. Subjects with specific chronic stable medical conditions, as noted above, may be included at the discretion of the Investigator and Sponsor.

4. Has a history of cancer (malignancy)

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

5. Subject has an estimated creatinine clearance of < 60 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is (for females multiply result by 0.85):

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

   When creatinine is measured in micromole/litre, use the following formula:

$$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L] x } 0.0113)}$$

6. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.
7. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV at Screening.
8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
9. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.
10. Has QTc interval >450 msec, has a history of risk factors for Torsades de Pointes (e.g., heart failure/cardiomyopathy or family history of Long QT Syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval at Screening.
11. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. Certain medications, such as antihypertensives and aspirin, are permitted, see Sections 5.1.2 and 5.5.

12. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Patients that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
13. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
14. Is a regular user of cannabis or any illicit drugs, or has a history of drug (including alcohol) abuse within approximately 6 months. Subjects must have a negative UDS prior to randomization.
15. Is any concern by the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial
16. Has a history of diabetic ketoacidosis in the last 12 months.
17. Has the diagnosis of hypoglycemia unawareness, or has had one or more severe hypoglycemic episodes associated with hypoglycemic seizures, comas or unconsciousness within 6 months prior to dosing.
18. Has used systemic (intravenous, oral, inhaled) glucocorticoids within 3 months of screening or is anticipated to require treatment with systemic glucocorticoids during study participation.
19. Has other major medical problems requiring medication (i.e., history of MI, hypercholesterolemia). Subjects on aspirin as prophylaxis may be enrolled, provided there is no history of MI or other thromboembolic event, or a history of coronary atherosclerosis. As noted above, subjects with other medical problems (i.e., gastroesophageal reflux disease) may be included in the trial at the discretion of the Investigator and Sponsor.
20. Has a known history of celiac disease or significant food allergy, at the discretion of the Investigator and Sponsor.
21. Has a history of hypersensitivity to pharmacologic insulins or to any of the inactive ingredients in regular human insulin, or to any E.coli-derived drug product.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

For Part 2 (T2DM):

1. Is under the age of legal consent
2. Is mentally or legally incapacitated, has significant emotional problems at the time of pretrial (screening) visit or expected during the conduct of the trial or has a history of clinically significant psychiatric disorder of the last 5 years. Subjects who have had situational depression may be enrolled in the trial at the discretion of the investigator.

3. Has a history of clinically significant endocrine (excluding diabetes mellitus), gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma may be enrolled in the trial at the discretion of the investigator. Subjects with specific chronic stable medical conditions, as noted above, may be included at the discretion of the Investigator and Sponsor.
4. Has a history of cancer (malignancy)

   Exceptions: (1) Subjects with adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix may participate in the trial; (2) Subjects with other malignancies which have been successfully treated ≥10 years prior to the pretrial (screening) visit where, in the judgment of both the investigator and treating physician, appropriate follow-up has revealed no evidence of recurrence from the time of treatment through the time of the pretrial (screening) visit (except those cancers identified at the beginning of exclusion criterion 4); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.
5. Subject has an estimated creatinine clearance of < 60 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is (for females multiply result by 0.85):

   $$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

   When creatinine is measured in micromole/litre, use the following formula:

   $$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L]} \times 0.0113)}$$

6. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.
7. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV at Screening.
8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
9. Has participated in another investigational trial within 4 weeks (or 5 half-lives), whichever is greater, prior to the pretrial (screening) visit. The window will be derived from the date of the last visit in the previous trial.
10. Has QTc interval >450 msec, has a history of risk factors for Torsades de Pointes (e.g., heart failure/cardiomyopathy or family history of Long QT Syndrome), has uncorrected hypokalemia or hypomagnesemia, is taking concomitant medications that prolong the QT/QTc interval at Screening.

11. Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of trial drug, throughout the trial (including washout intervals between treatment periods), until the post-trial visit. Certain medications are permitted, including antihypertensives, aspirin, and HMG-CoA reductase inhibitors (see Sections 5.1.2 and 5.5).
12. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Patients that consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.
13. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine) of coffee, tea, cola, energy-drinks, or other caffeinated beverages per day.
14. Is a regular user of cannabis or any illicit drugs, or has a history of drug (including alcohol) abuse within approximately 6 months. Subjects must have a negative UDS prior to randomization.
15. Is any concern by the investigator regarding the safe participation of the subject in the trial or for any other reason the investigator considers the subject inappropriate for participation in the trial
16. Has other major medical problems requiring medication (i.e., history of MI, hypercholesterolemia). Subjects on aspirin as prophylaxis may be enrolled, provided there is no history of MI or other thromboembolic event, or a history of coronary atherosclerosis. As noted above, subjects with other medical problems (i.e., gastroesophageal reflux disease) may be included in the trial at the discretion of the Investigator and Sponsor.
17. Has the diagnosis of hypoglycemia unawareness, or has had one or more severe hypoglycemic episodes associated with hypoglycemic seizures, comas or unconsciousness within 6 months prior to dosing.
18. Has a known history of celiac disease or significant food allergy, at the discretion of the Investigator and Sponsor.
19. Has used systemic (intravenous, oral, inhaled) glucocorticoids within 3 months of screening or is anticipated to require treatment with systemic glucocorticoids during study participation.
20. Has been treated with an SGLT2 inhibitor (gliflozins), thiazolidinedione or GLP-1 receptor agonist within the past three months.
21. Has a history of hypersensitivity to pharmacologic insulins or to any of the inactive ingredients in regular human insulin, or to any E.coli-derived drug product.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 3.

Table 3 Trial Treatment

Drug, Vaccine, Biologic, Device, etc.	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period Regimen	Use
MK-5160	Potency: 20 mg/mL	Daily for 12 days	Subcutaneous	Parts 1 & 2 all panels	Experimental
Glargine	100 U/mL	Daily for 12 days	Subcutaneous	Parts 1 & 2 all panels	Active comparator
Dextrose	20% solution; adjusted to maintain the various glycemic levels at 100 mg/dL	Continuous infusion for 6-30 hours (as needed to maintain blood sugar at 100 mg/dL	Intravenous	Parts 1 & 2 all panels	Glucose Clamp Assessment
Placebo	Not applicable	Daily for 12 days	Subcutaneous	Parts 1 & 2 all panels	Comparator

Trial treatment should begin on the day of treatment allocation/randomization or as close as possible to the date on which the subject is allocated/assigned.

All supplies indicated in Table 3 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. Specific calculations or evaluations required to be performed in order to administer the proper dose to each subject are outlined in a separate document provided by the Sponsor.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Dose escalation decisions will be based on key safety variables including, vital signs, 12-lead ECG, laboratory safety tests, and adverse events from the previous dose levels up to at least 24 hours (or longer depending on the compound). Pharmacokinetic and pharmacodynamic data may be included in the dose escalation decisions. See Background & Rationale - Section 4.0.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, subjects may:

- receive the same dose level to further explore safety and tolerability at that level;
- receive a lower dose of the trial drug;
- receive the same or lower dose as a divided dose; or
- receive a lower dose with or without food.

Or, dosing may be stopped. Subject discontinuation criteria are outlined in Section 5.8.

Prior to each treatment, the clinical and laboratory safety parameters from the previous dose level will be reviewed by the investigator and discussed with the Sponsor to permit a decision on whether to advance to the next higher dose level. No dose escalation will occur without the joint agreement of the investigator and the Sponsor.

5.2.2 Timing of Dose Administration

MK-5160 or glargine will be prepared and dosed in the morning following a fast of at least 8 hours per the instructions outlined in the Study Operations Manual.

5.2.3 Trial Blinding

A double-blinding technique will be used. MK-5160 and glargine will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who is involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

Subjects will be administered placebo, as well as MK-5160 or glargine, so that subjects receive two injections – MK-5160 and glargine-matched placebo, or glargine and MK-5160-matched placebo.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Subjects will be assigned randomly according to a computer-generated allocation schedule. See sample in Table 4.

Table 4 Sample Allocation Schedule

Part 1 (T1DM Patients)			
Subjects	**Panel A**	**Panel B**	**Panel C**
N=6 N=2	MK-5160 16 nmol/kg SC Glargine 0.4 U/kg		
N=6 N=2		MK-5160 32 nmol/kg SC Glargine 0.4 U/kg	
N=6 N=2			MK-5160 ≤64 nmol/kg SC Glargine 0.4 U/kg
Part 2 (T2DM Patients)			
Subjects	**Panel D**	**Panel E**	**Panel F**
N=6 N=2	MK-5160 16 nmol/kg SC Glargine 0.6 U/kg		
N=6 N=2		MK-5160 32 nmol/kg SC Glargine 0.6 U/kg	
N=6 N=2			MK-5160 ≤64 nmol/kg SC Glargine 0.6 U/kg
Subjects will participate in only one panel To maintain blinding, subjects will receive two injections at each administration – one active (MK-5160 or glargine) and one placebo due to potential differing volumes of the active treatments.			

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

Ibuprofen may be used for minor ailments without prior consultation with the Sponsor, and is permissible to have been taken prior to the trial.

Listed below are specific restrictions for concomitant therapy during the course of the trial:

1. Subjects on a sulfonylurea or alpha-glucosidase inhibitors may be included in the trial, provided these medications are stopped at least one week prior to checking into the site.
2. Subjects on metformin and/or DPP-4 inhibitor must continue their home dose for the duration of the trial.

3. SGLT2 inhibitors (gliflozins), thiazolidinediones and GLP-1 agonists are not allowed. Subjects who have taken these medications within three months of screening are excluded from the trial.
4. Subjects with a diagnosis of hypercholesterolemia are excluded from Part 1. Lipid-lowering medications (HMG-CoA reductase inhibitors) would, therefore, not be allowed in subjects in Part 1. Subjects in Part 2 (T2DM) may remain on lipid-lowering medications.
5. Subjects on aspirin for thrombosis prophylaxis, without history of MI, other thromboembolic event or atherosclerosis requiring procedural intervention, may remain on aspirin for the duration of the trial.
6. Beta-blockers and loop diuretics are not allowed. Subjects on these medications will be excluded.
7. Systemic glucocorticoids are not allowed. Subjects on inhaled or topical glucocorticoids may be allowed, at the discretion of the Investigator and Sponsor.
8. Other concomitant medications not addressed above (i.e., proton pump inhibitors, anti-depressants) may be allowed, at the discretion of the Investigator and Sponsor.

5.6 Rescue Medications & Supportive Care

To ensure subject safety, this study is conducted at an experienced Phase I clinical research unit with ACLS-trained medical staff available to intervene in case of severe hypoglycemia or diabetic ketoacidosis. Resuscitative equipment and rescue treatment will be available at the clinical research unit during the trial. In addition, the clinical research unit has immediate access to a full service acute-care hospital to facilitate rapid institution of medical intervention if required. Refer to Appendix 12.6 for additional details on intervention for hypo- and hyperglycemia.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

On **clamp days**, i.e. Days 1 and 12, subjects will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration/clamp procedure. Subjects will remain fasted from all food and drinks except water until approximately 1 hour after the end of the clamp procedure. Standardized, uniform meals and snack(s) will be provided by the investigator in accordance with the site's standard schedule. Subjects will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each full pharmacokinetic sampling day in each panel.

On **intermediate days** (Days 2-11), subjects will fast from all food and drinks, except water, for at least 8 hours prior to trial drug administration. Subjects may eat after dosing on non-clamp days. Meals and snacks will be standardized with respect to caloric content, composition and timing. On Day 7, all subjects will fast after the afternoon snack (i.e. there will be no dinner or evening snack). Subjects will remain fasted overnight until after the morning blood draw and dosing. On Day 9, subjects who tolerated the fasting on Day 7 (at the discretion of the Investigator) will undergo similar fasting after the afternoon snack, with

no dinner or evening snack. Subjects may consume water during this time, and will be monitored for hypoglycemia.

5.7.2 Alcohol, Caffeine, Tobacco, Activity

5.7.2.1 Alcohol Restrictions

Subjects will refrain from consumption of alcohol 24 hours prior to the pre- and post-trial visits, from 24 hours prior to trial drug administration, while domiciled in the clinical unit. At all other times (between screening and domiciling, and between Days 15-19), alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.7.2.2 Caffeine Restrictions

Subjects will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the pre- and post-trial visits. Subjects will refrain from consumption of caffeinated beverages or xanthine-containing products while domiciled and during the days immediately afterward (Days 15-19).

5.7.2.3 Smoking Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the trial.

5.7.2.4 Activity Restrictions

Subjects will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the pre-trial (screening) visit until administration of the initial dose of trial drug, and until the post-trial visit. During the domiciling period, subjects will engage in activity as per site specifications.

5.7.2.5 Contraception

Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 90 days after the last dose of trial drug. Males should use a condom. Female partners must additionally use one of the following methods if they are not pregnant: hormonal contraception, intra-uterine device, diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male subjects must also agree to not donate sperm during the study and for a period of 90 days after the last dose of study drug.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment, but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.
- The subject interrupts trial medication administration for more than 1 consecutive day or has 2 cumulative missed doses.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the subject at unnecessary risk from continued administration of study drug/vaccine.
- The subject has a positive urine drug screen at any time during the course of the trial.
- The subject has liver function test (ALT and/or AST) value changes of $\geq$3 times the upper limit of normal that are not associated with any plausible cause. May consider discontinuation of study.
- The subject has QTcF prolongation meeting pre-specified criteria (see Appendix 12.4).

For subjects who are discontinued from treatment, all applicable discontinuation activities will be performed according to Section 7.1.4.1 – Withdrawal/Discontinuation, or if available, Protocol Clarification Letter.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the study.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

If a subject discontinues from trial treatment or withdraws from the trial, a replacement subject may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced. The replacement subject will be assigned a unique treatment/randomization number. The trial site should contact the Sponsor for the replacement subject's treatment/randomization number.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

A trial may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy or biologic data or other items of interest, prior to a final decision on continuation or termination of the trial. It may be necessary to keep the trial open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the trial. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall trial end will then not be identified until the Sponsor has made the decision to end the trial following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be appraised of the maximum duration of the trial beyond the last subject out and the justification for keeping the trial open.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Flowchart – Overall Study [a]

	Screening	Predose				Treatment Period												Postdose			Post-trial
	Screening [b] (Up to -30)	D -4	D -3	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D 10	D 11	D 12	D 13	D14 [q]	D15 - 19	D 28 (+/- 3 days)
Administrative Procedures																					
Informed Consent	X																				
Informed Consent for Future Biomedical Research	X																				
Inclusion/Exclusion Criteria	X																				
Subject Identification Card	X																				
Medical History	X																				
Concomitant Medication Review	X																				
Admission to the Unit		X																			
Discharge from the Unit																			X[r]		
Clinic Procedures/Assessments																					
Full Physical Examination	X				X														X		
Height	X																				
Weight [c]	X				X														X		
12-Lead Electrocardiogram [d]	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs (heart rate, blood pressure) [e]	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Orthostatic Vital Signs (heart rate, blood pressure)	X					X					X						X				
Vital Signs (respiratory rate, oral/tympanic temperature)	X					X					X						X				
Standard Meals		X	X	X	X		X	X	X	X	X	X[n]	X	X[n]	X	X		X	X		
MK-5160 or Glargine Administration						X	X	X	X	X	X	X	X	X	X	X	X				
Injection site local tolerability assessment [f]						X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events Monitoring [g]	X	X----------																			X
Laboratory Procedures/Assessments																					
Hematology	X				X		X			X				X				X			X
Urinalysis	X				X		X											X			X
Chemistry	X				X		X			X				X				X			X
Urine Pregnancy Test – if applicable	X																				X
Serum Follicle Stimulating Hormone (FSH) - if applicable [h]	X																				
Urine Drug Screen [i]	X	X																			

	Screening	Predose				Treatment Period												Postdose			Post-trial
	Screening [b] (Up to -30)	D -4	D -3	D -2	D -1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D 10	D 11	D 12	D 13	D14 [q]	D15 - 19	D 28 (+/- 3 days)
Breath Alcohol Assessment	X	X																			
HIV/Hepatitis Screen (per site SOP)	X																				
Blood for Genetic Analysis[j]						X															
NEFA						X	X	X			X						X	X			
Glycerol						X	X	X			X						X	X			
Ketones (ß-hydroxybutyrate)					X	X	X	X			X				X		X	X			
Glucagon					X		X						X		X			X			
Blood for Serum C-peptide[s]	X																				
Blood for triglycerides	X				X	X	X			X				X			X	X			
Blood for Serum Anti-glargine (Insulin) Antibody/ /Immunogenicity Assay					X														X		X
Blood for Serum Anti-MK-5160 Antibody/Immunogenicity Assay					X														X		X
Pharmacokinetics Evaluations																					
Blood for Plasma MK-5160 and/or Metabolites assay or Glargine [k,l]						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacodynamic Evaluations																					
IV infusion of insulin					X											X					
IV infusion of dextrose					X											X					
Euglycemic Clamp/Infusion of Glucose [m]						X											X				
Blood for Glucose Bedside Analysis [o]						X											X				
Fingerstick Glucose Testing[p]		X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X		
Continuous Glucose Monitoring		X----------X																			

a. All subjects will participate in only 1 Panel.
b. Screening should be done within 30 days of Day 1.
c. Weight will be obtained with the subjects shoes off, jacket or coat removed, with a single calibrated scale. Weight obtained at baseline (Day -1) will be used for determining amount of drug to be administered.
d. All ECGs will be obtained in triplicate at least 1-2 minutes apart daily around the same time on non-clamp days (predose). On Day -1, ECGs will be obtained. The mean of these measurements will be used as the baseline. During the clamp procedure (see Clamp Flow Chart) ECG measurements will be taken in triplicate at predose, 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12.0 hr, 18.0 hr, 24.0 hr, 30.0 hr and 36.0 hr. Measurements will also be collected at Post clamp.
e. At screening, the mean of 3 measurements taken within a 10-minute period (all 3 sets completed within 10 minutes) will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator. On Day 1, HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within approximately 60 minutes prior to dosing MK-5160/glargine. The mean of these measurements will be used as the baseline. On the day of clamp procedures, post-dose Vital Sign assessments will be done at 30 min (0.5h), 60 min (1h), 180 min (3.0 hr), 360 min (6 hr), 9.0 hr, 12.0 hr, 18.0 hr, 24.0 hr, 30 hr, and 36 hr.
f. Injection site local tolerability assessment will be recorded as an AE if any reactions are identified.
g. Adverse experiences (including serious adverse events) will be reported from the signing of informed consent through 33 days (5 days from Day 28) following cessation of treatment.
h. For postmenopausal females without menses for at least 1 year.
i. Screening UDS is mandatory, any additional UDS are conducted per site SOP
j. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
k. Leftover main study plasma will be stored for future biomedical research if the subject consents to future biomedical research.
l. Blood for Plasma MK-5160 Assay will be collected daily and at the following timepoints on the Day 1 clamp: -15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720, and 1440 minutes following start of injection (i.e. - 15 min, 10min, 30min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 24 h, after s.c. dose). For the second clamp on Day 12, the following timepoints will be collected: -15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720, 1440 minutes (24h, Day 13), 48h (Day 14), 72h (Day 15), 96h (Day 16), 120h (Day 17) and 168h (Day 19) following start of injection. Blood will also be collected at Post-trial (28 days). Exploratory analysis for MK-5160 metabolites may be performed.
m. Refer to the Study Operations Manual for clamp procedures including how to initiate and titrate glucose infusion levels to target and maintain plasma glucose at 100 mg/dL. Glucose infusion will be discontinued at the discretion of the investigator as detailed in the Study Operations Manual. The duration of the infusion may be shorter or longer than specified.
n. On these days, subjects will only be fed these meals: Day 7 – breakfast and lunch; Day 9 – breakfast and lunch.
o. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and every 1 to 10 minutes. If necessary, collection may be performed more frequently at the investigator's discretion.
p. Fingersticks should occur before meals, before bedtime (~11:00 PM), and as needed overnight.
q. Subjects are discharged on Day 14, but return to the CRU on Day 15, Day 16, Day 17 and Day 19 for PK draws.
r. Subjects may elect to stay in the unit through Day 19 if the Investigator and the subject feel there is a risk in being unable to return for the PK visits from Days 15-19.
s. For T1DM subjects only.

Clamp Flow Chart (Day 1 and Day 12)

	Pre-dose	0	1h	2h	4h	6h	9h	12h	18h	24h	30h	36h
Clinic Procedures/Assessments												
12-Lead Electrocardiogram[a]	X----------X						X	X	X	X	X	X
Semi-Recumbent Vital Signs (heart rate, blood pressure) [b]	X----------X						X	X	X	X	X	X
Orthostatic Vital Signs (heart rate, blood pressure)	X							X				
Vital Signs (respiratory rate, oral/temporal/tympanic temperature)	X							X[g]				
MK-5160/Glargine Administration		X										
Injection site local tolerability assessment [c]		X										
Adverse Events Monitoring	X----------X											
Laboratory Procedures/Assessments												
Hematology										X		
Urinalysis										X		
Chemistry										X		
Blood for Genetic Analysis	X											
NEFA	X			X		X		X	X	X		
Glycerol	X			X		X		X	X	X		
Ketones	X					X				X		X
Glucagon										X		
Triglycerides	X							X		X		
Pharmacokinetics Evaluations												
Blood for PK MK-5160 or Glargine assay[d]	X----------X											
Pharmacodynamic Evaluations												
Euglycemic Clamp/ Infusion of Glucose [e]		X----------X										
Blood for Glucose Bedside Analysis [f]	X----------X											

a. During the clamp period post baseline ECG measurements will be taken at predose (within 2 hours prior to dosing), 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12.0 hr, 18.0 hr, 24.0 hr, 30.0 hr and 36.0 hr.
b. On clamp days (D1 and D12) Vital Sign assessments will be done at predose (within 2 hours prior to dosing), 30 min (0.5h), 60 min (1h), 180 min (3.0 hr), 360 min (6 hr), 9.0 hr, 12.0 hr, 18.0 hr, 24.0 hr, 30 hr, and 36 hr.
c. Injection site local tolerability assessment will be recorded as an AE if any reactions are identified.
d. Blood for Plasma MK-5160 Assay will be collected daily and at the following timepoints on the Day 1 clamp: -15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720, and 1440 minutes following start of injection (i.e. - 15 min, 10min, 30min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 10h, 12h, and 24 h, after s.c. dose). For the second clamp on Day 12, the following timepoints will be collected: -15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 480, 600, 720, 1440 minutes (24h, Day 13), 48h (Day 14), 72h (Day 15), 96h (Day 16), 120h (Day 17) and 168h (Day 19) following start of injection. Blood will also be collected at Post-trial (28 days). Exploratory analysis for MK-5160 metabolites may be performed. Leftover main study plasma will be stored for future biomedical research if the subject consents to future biomedical research.
e. Refer to the Study Operations Manual for clamp procedures including how to initiate and titrate glucose infusion levels to target and maintain plasma glucose at 100 mg/dL. Glucose infusion will be discontinued at the discretion of the investigator as detailed in the Study Operations Manual. The duration of the infusion may be shorter or longer than the 24 hours.
f. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and every 1 to 10 minutes. If necessary, collection may be performed more frequently at the investigator's discretion.
g. May be collected +/- 30 minutes from timepoint

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 14 days before starting the trial.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)

Administration of trial medication will be witnessed by the investigator and/or trial staff.

7.1.2 Clinical Procedures/Assessments

Physical Exam:

The physical exam assessments will be defined and conducted per the site SOP.

Body Weight and Height

Body weight and height will be obtained with the subjects shoes off, jacket or coat removed with a single calibrated scale.

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m2). Document this BMI to the nearest 0.1 kilogram/(meter)2.

Weigh the subject's after an overnight fast, after voiding, while in a gown or underwear, without shoes, on a calibrated scale. Document this weight in kilograms (kg), to the nearest 0.1 kg.

Measure the subject's height on a calibrated stadiometer, without shoes. Document this height in meters, to the nearest 0.01 meter (0.01 meter = 1 centimeter, cm).

12-Lead ECG

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra.

Subjects should be resting in the semi-recumbent for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fredericia.

If repeat ECGs are required the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each subject with an ECG skin marker pen to ensure reproducible electrode placement.

Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 1-2 hours prior to dosing MK-5160. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

During each treatment period, if a subject demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the mean QTc interval increase from baseline for any postdose time point is ≥60 msec, the subject will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a Cardiac or Intensive Care Unit) is available.

Monitoring of potassium levels at the bedside will be performed as deemed necessary at the discretion of the investigator.

If the subject has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the subject should be immediately transferred to an acute care setting for definitive therapy.

A study cardiologist should be arranged by the Principal Investigator to be available as needed to review ECG tracings with abnormalities.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual subject and should be the same for all subjects.

Vital Sign Measurements (Heart Rate and Blood Pressure)

Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include heart rate (HR) and blood pressure (BP). The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements.

The predose (baseline) HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 60 minutes of dosing MK-5160/glargine. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed).

Orthostatic vital signs (HR and BP) will also be obtained. Subjects should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic vital signs.

Glucose Clamp

The glucose clamp technique will be applied in this study, with each subject receiving an infusion of exogenous glucose (20% dextrose) during and after study drug administration. Glucose infusions will be adjusted to maintain a stable plasma glucose target in the euglycemic range (100 mg/dL). The clamp will be maintained to characterize washout of the PD effect and to ensure safety. The clamp will be discontinued at the discretion of the investigator when the GIR appears stable which may extend to 24 hours or longer after the initiation.

Plasma glucose concentrations will be frequently measured by bedside analysis as a guide for adjusting the rate of glucose infusion. Additional details are provided in the Study Operations Manual.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle Stimulating Hormone (FSH)
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis B/C Screening
Platelet count	Alanine aminotransferase (ALT)	Protein	HIV
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Urine Drug Screen
	Bicarbonate	Microscopic exam, if abnormal results are noted	Breath alcohol assessment
	Calcium		C-peptide
	Chloride		Nonesterified Fatty Acids (NEFA). Also known as Free Fatty Acids (FFA).
	Creatinine		Ketones (β-hydroxybutyric acids)
	Glucose		Glycerol
	Magnesium		Glucagon
	Potassium		Triglycerides

Hematology	Chemistry	Urinalysis	Other
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

Pre-trial (screening) and post-trial laboratory safety tests will be performed after at least an 8-hour fast. Fasting is required for the pre-dose (Day -1) laboratory safety tests. Pre-dose laboratory procedures can be conducted up to 30 hours prior to dosing, and must be reviewed (with the exception of C-peptide, insulin, NEFA, ketones, glucagon, and glycerol) prior to dosing on Day 1.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which plasma and/or urine samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be collaboratively determined by the Department of Quantitative Pharmacology and Pharmacometrics (QP2) and the appropriate department within Early-Stage Development, (e.g., samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

7.1.3.2.1 Blood Collection for Plasma MK-5160

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.2.2 Blood Collection for Glargine

Sample collection, storage and shipment instructions for plasma samples will be provided in the operations/laboratory manual.

7.1.3.2.3 Blood Collection for Plasma Glucose (Bedside Analysis)

Ambient glucose concentrations from plasma will be recorded frequently (approximately 5 minutes apart) by GlucoScout, or equivalent, at the bedside per site operating procedures to guide titration of glucose infusions in achieving specified glycemic target levels. Additional glucose measurements will be assessed using Yellow Springs Instrument (YSI) per the study operations manual.

Glucose infusion rates will be recorded frequently throughout the infusion/clamp procedure per site standard operating procedures.

7.1.3.2.4 Blood Collection for Anti-MK-5160 and Anti-Glargine (Insulin) Antibody/Immunogenicity Assay

Serum samples will be collected to assess the presence of anti-MK-5160/insulin antibodies. Sample collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

7.1.3.4 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main study plasma from MK-5160 and/or metabolites or glargine stored for future research.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

The investigator or trial coordinator must notify the Sponsor when a subject has been discontinued/withdrawn from the trial. If a subject discontinues for any reason at any time during the course of the trial, the subject may be asked to return to the clinic (or be contacted) for a post-trial visit (approximately 14 days after the last protocol-specified procedure is performed) to have the applicable procedures conducted. However, the investigator may decide to perform the post-trial procedures at the time of discontinuation or as soon as possible after discontinuation. If the post-trial visit occurs prior to 14 days after the last protocol-specified procedure is performed, the investigator should perform a follow-up phone call 14 days after the last protocol-specified procedure to determine if any adverse events have occurred since the post-trial clinic visit. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD. Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines

7.1.4.2 Subject Blinding/Unblinding

When the investigator or delegate needs to identify the drug used by a subject in case of emergency e.g., the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the intensity/toxicity grade of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc. Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

Treatment/Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

At the end of the trial, random code/disclosure envelopes or lists and unblinding logs are to be returned to the Sponsor or designee.

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) on Day -4 prior to the scheduled day of trial drug administration on Day 1 and remain in the unit until Day 14. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

7.1.4.4 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

ECG machine, equipment for Vital Signs measurements, glucometers, Yellow Springs Instrument (YSI) glucose analyzer, GlucoScout, and syringe/infusion pumps for administering glucose and study drugs.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Within 30 days prior to day 1, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Subjects may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the protocol flow chart, including consent review. Rescreen procedures cannot be conducted the day prior to treatment allocation/randomization if there are Day -1 procedures planned per protocol.

7.1.5.2 Treatment Period Visit

Subcutaneous MK-5160 or glargine will be administered as a daily injection from Day 1 to Day 12.

Exogenous glucose will also be infused concurrently with adjustments as needed to maintain a stable glucose concentration predefined by the subject's baseline fasting glucose during the clamp procedure and longer if necessary. Details of this euglycemic clamp technique are outlined in the Study Operations Manual.

7.1.5.3 Post-Trial

Subjects will be required to return to clinic approximately 16 days (+/ 3 days) after the last dose of trial drug for the post-trial visit. If the post-trial visit occurs less than 16 days after the last dose of trial drug, a subsequent follow-up phone call should be made at 16 days post the last dose of trial drug to determine if any adverse events have occurred since the post-trial

clinic visit. Subjects will be required to return to clinic approximately 16 days (+/- 3 days) post final dose (Day 28) for collection of additional anti-drug antibodies (ADA) and anti-insulin antibodies (AIA) samples.

If a subject has a positive titer at the 28 day follow-up visit, an additional sample will be drawn approximately 56 days (+/- 5 days) after the completion of dosing. At the same time, a fasting plasma glucose sample will be drawn from the subject and an evaluation of possible signs and symptoms of hyperglycemia will be conducted. If medically required the subject will be referred to an endocrinologist for further treatment.

Additional follow-ups will be conducted in intervals of approximately 3 months (+/- 5 days) in subjects with detectable ADAs/AIAs until one of the following occurs:

a) subject no longer has detectable ADAs/AIAs,

b) ADAs/AIAs are persistent and stable (titers within 2 to 3-fold of each other) on 3 consecutive checks at 3 month intervals,

c) return to baseline levels (i.e., within 2 to 3-fold of predose)

An additional fasting plasma glucose sample will be drawn at each time subjects return for ADA/AIA follow-up, and an evaluation of possible signs and symptoms of hyperglycemia will be conducted. Subjects will be referred to an endocrinologist if medically required.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample collection for MK-5160 and glargine is the critical procedure as is the glucose clamp procedure.

At any post-dose timepoint, the blood sample for MK-5160 needs to be collected as close to the exact timepoint as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection as outlined in Table 6 below

Table 6 PK (Blood) Collection Windows

PK collection relative to dose	PK Collection Window
hr	+/- 5 min
> 1 hr	+/- 15 min
24 hr (daily)	+/- 30 min
> 48 hr after last dose	+/- 2 hours

- Non-clamp day standard safety evaluations: (vital signs & ECG) - +/- 3 hrs (predose); (laboratory safety tests & physical exam) - +/- 6 hrs
- Clamp day standard safety evaluations (vital signs, ECG, laboratory safety tests, physical exam): +/- 30 mins
- Pharmacodynamic or other protocol specific measurements, or modification to any of the above windows:
    - NEFA, glycerol, glucagon, triglycerides, C-peptide, and endogenous insulin: +/- 30 minutes
    - ADA/AIA: +/- 6 hours
- Study drug administration: +/- 30 mins

7.1.5.5 Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters

This is a Phase I assessment of MK-5160 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase I clinical trials. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined below may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the trial drug administered in any given period/panel
- Interchange of doses between panels
- Entire period(s) or panel(s) may be omitted
- Decrease in the duration of trial drug administration (e.g., number of days)
- Remove a planned pharmacokinetic pause if agreed by Sponsor and investigator if no further increases in total daily dose
- Addition of pharmacokinetic pause
- Addition of operational pause
- Decrease in the target glycemic level to be maintained during glucose infusion/clamp procedure
- Decrease in number of PK sampling timepoints
- Modification of the PK/PD sample processing and shipping details based on newly available data
- Modification of urine sample collection to another panel or period

The pharmacokinetic/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the trial based on newly available pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL (NOTE: Never more than 50 mL) of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single subject will not exceed the maximum allowable volume during his/her participation in the entire trial (Section 12.3).

The timing of procedures for assessment of safety procedures (e.g., vital signs, ECG, safety laboratory tests, etc.) currently outlined in the protocol may be modified during the trial based on newly available safety, tolerability, pharmacokinetic or pharmacodynamic data (e.g., to obtain data closer to the time of peak plasma concentrations). Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information (e.g., adding creatinine kinase to serum chemistry panel that was already drawn. These changes will not increase the number of trial procedures for a given subject during his/her participation in the entire trial.

It is understood that the current trial may employ some or none of the alterations described above. Any alteration made to this protocol to meet the trial objectives must be detailed by the Sponsor in a letter to the Trial File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

For randomized subjects only, all adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by investigator if they are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 19 days following cessation of treatment, (5 days after Day 28) all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

The subject has taken (accidentally or intentionally) any drug administered as part of the protocol and exceeding the dose as prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be

reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse EventsAdverse Events and Incidents to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 19 days following cessation of treatment (5 days after Day 28), any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

   It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

1. any suspected allergic reaction, including the following:
    - Any skin reaction, skin eruption, and/or rash occurrence in a study subject following administration of study drug,
    - Study-drug related systemic reactions or study drug-related hypersensitivity reactions (e.g., anaphylaxis, angioedema).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 7. The investigator's assessment of causality is required for each adverse event. Refer to Table 7 for instructions in evaluating adverse events.

Table 7 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details can be found beginning in Section 8.2).

Statistical Methods

Safety:

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate. Results will be summarized separately by study part.

Pharmacodynamics

Individual maximal GIR values (GIRmax) based on LOESS smoothed data will be analyzed in a linear mixed effects model with fixed effects for treatment (i.e. glargine, MK-5160 Dose Level 1, MK-5160 Dose Level 2, MK-5160 Dose Level 3), day (Day 1, Day 12) and treatment by day interaction, a continuous covariate for BMI, and a random effect for subject. A separate model will be used for each patient population (T1DM, T2DM).

GIRmax means and 95% confidence intervals for each treatment/day will be calculated from the model. To test the primary hypothesis, the posterior probability that the true mean GIRmax level at steady state is within 1.5 and 4.5 mg/kg/min will be calculated for each MK-5160 dose on Day 12 using a non-informative prior. If this posterior probability exceeds 70% for at least one safe and well tolerated dose of MK-5160 for each population, then the primary research hypothesis will be supported.

Between treatment GIRmax comparisons (MK-5160 versus glargine) will be performed for each dose of MK-5160 and on each day, using the model.

Pharmacokinetics

Non-compartmental Analysis (NCA) based geometric means and 95% confidence intervals will be provided for Cmax, AUC0-24hr, Css and CL by treatment, day and population. The geometric mean accumulation ratio (Day 12 PK / Day 1 PK) and 90% CI will be calculated for Cmax and AUC0-24hr.

Scatterplots of individual PK values (Steady state AUC0-24hr, Cmax, Css) versus BMI will be plotted for each patient population.

Individual values will be listed for each PK parameter by treatment and day and the additional following (NCA-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale). For Tmax, only median, minimum and maximum will be calculated.

Pharmacokinetic endpoints following administration with glargine may be summarized in a similar fashion, as appropriate.

Power

Pharmacodynamics

This is the first study of MK-5160 in a diabetic patient population, and as such no variance estimates exist other than those from a single dose study in normal healthy volunteers (P001). In order to provide an approximate estimate of power, the variability observed in P001 has been used for the power calculations presented below (Table 8). [redacted]

Table 8 Probability of Supporting Primary PD Hypothesis

Target GIRmax (mg/kg/min)	True GIRmax	Probability of Supporting Hypothesis
(1.5, 4.5)	1	2%
	1.5	30%
	2	86%
	2.5	99%
	3	99%
	3.5	99%
	4	86%
	4.5	30%
	5	2%
The calculations above were based on [redacted] and N=6 per dose, and a posterior probability threshold of 70%.		

8.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Clinical Pharmacology Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics (QP2), and Translational Pharmacology Departments of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

8.3 Hypotheses/Estimation

Primary:

At a dose with sufficient safety, the mean steady-state maximum level of GIR (GIRmax) after MK-5160 administration in both T1 and T2 DM patients is between 1.5 and 4.5 mg/kg/min.

8.4 Analysis Endpoints

Primary:

Safety

The primary safety endpoints in this study will include all types of adverse experiences, in addition to laboratory safety assessments, ECGs, and vital signs.

Pharmacodynamics

The primary pharmacodynamic variable in this study is the glucose infusion rate (GIR) required to maintain plasma glucose at each subjects' individual clamp target, following administration of MK-5160 or glargine. To assess the primary hypothesis, individual maximal GIR (GIRmax) values at steady state (Day 12) will be used. Prior to obtaining the maximal GIR values, data will be smoothed (LOESS) to minimize variability and the potential impact of transient outliers influencing the estimation. The default smoothing function in SAS PROC LOESS, which selects an optimal smoothing parameter based on minimizing a bias corrected AIC criterion, will be used to fit an optimal smoothing function for each subject.

Additional clamp endpoints that may be analyzed in a similar fashion as above include GIR AUC endpoints over the entire clamp timeframe (0-24 hours) as well as various subfractions of interest (e.g. 0-12, 12-24 hours and 24-end for the Day 12 clamp), though these would be based on raw data and not LOESS smoothed.

Secondary:

Pharmacokinetics

The pharmacokinetic variables of interest include Cmax, Css, Steady State AUC0-24hr, CL, Tmax and t1/2 of MK-5160 after SC administration. Similar endpoints for glargine may also be of interest, as appropriate.

Exploratory:

Pharmacodynamics

The exploratory pharmacodynamic endpoints in this study include FFA, glycerol, triglycerides, β-hydroxybutyrate, glucagon and fasting morning glucose levels, following SC administration of MK-5160 or glargine. Baseline is the Day 1 Predose value.

8.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All subjects will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (AST) – All subjects who received at least one dose of the investigational drug. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP) – The set of data generated by the subset of subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol deviations. Major protocol deviators will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least one treatment will be included in the primary analysis dataset. This population will be used for the PK and PD analyses.

8.6 Statistical Methods

Primary

Safety:

Incidence of adverse experiences will be descriptively summarized. Summary statistics and plots will be generated for the change from baseline values in the vital signs, ECG parameters, and selected laboratory safety parameters for subjects, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Summary statistics for the raw laboratory safety tests, ECGs, and/or vital signs may also be computed, as deemed clinically appropriate. Results will be summarized separately by study part.

The incidence and nature of nighttime and other episodes of potential hypoglycemia, using fingerstick glucose levels and CGM data will be summarized using descriptive statistics. Modeling techniques may be employed as needed.

Pharmacodynamics

Individual maximal GIR values (GIRmax) based on LOESS smoothed data will be analyzed in a linear mixed effects model with fixed effects for treatment (i.e. glargine, MK-5160 Dose Level 1, MK-5160 Dose Level 2, MK-5160 Dose Level 3), day (Day 1, Day 12) and treatment by day interaction, a continuous covariate for BMI, and a random effect for subject. A separate model will be used for each patient population (T1DM, T2DM).

GIRmax means and 95% confidence intervals for each treatment/day will be calculated from the model. To test the primary hypothesis, the posterior probability that the true mean GIRmax level at steady state is within 1.5 and 4.5 mg/kg/min will be calculated for each MK-5160 dose on Day 12 using a non-informative prior. If this posterior probability exceeds

70% for at least one safe and well tolerated dose of MK-5160 for each population, then the primary research hypothesis will be supported.

Between treatment GIRmax comparisons (MK-5160 versus glargine) will be performed for each dose of MK-5160 and on each day, using the model.

Additional clamp endpoints that may be analyzed in a similar fashion as above include GIR AUC endpoints over the entire clamp timeframe (0-24 hours) as well as various subfractions of interest (e.g. 0-12, 12-24 hours), though these would be based on raw data and not LOESS smoothed.

Secondary

Pharmacokinetics

NCA based geometric means and 95% confidence intervals will be provided for Cmax, AUC0-24hr, Css and CL by treatment, day and population. The geometric mean accumulation ratio (Day 12 PK / Day 1 PK) and 90% CI will be calculated for Cmax and AUC0-24hr.

Scatterplots of individual PK values (Steady state AUC0-24hr, Cmax, Css) versus BMI will be plotted for each patient population.

Individual values will be listed for each PK parameter by treatment and day and the additional following (NCA-based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale). For Tmax, only median, minimum and maximum will be calculated.

Pharmacokinetic endpoints following administration with glargine may be summarized in a similar fashion, as appropriate.

Exploratory

Pharmacodynamics

Plasma FFA, glycercol, triglycerides, β-hydroxybutyrate, glucagon and fasting morning glucose levels, following SC administration of MK-5160 or glargine will be summarized with descriptive statistics and plotted over time. More formal treatment comparisons (MK-5160 versus glargine) may also be performed. Baseline is the Day 1 Predose value.

Pharmacokinetics/Pharmacodynamics

Exploratory PK/PD plots linking PD measures (GIR, Glucose, FFA and other secondary PD measures) to PK measures (concentration at different timepoints, Cmax, steady state AUC0-24hr) may be plotted as deemed necessary. MK-5160 PK/PD relationship will be explored using an integrated PK/PD modeling approach as necessary.

8.7 Multiplicity

There is only one testable research hypothesis in this study. Formal statistical testing with associated p-value cut-offs centered around controlling Type-I error rates will not be used in assessing this hypothesis; hence no multiplicity adjustment is required or proposed.

8.8 Sample Size and Power Calculations

Pharmacodynamics

This is the first study of MK-5160 in a diabetic patient population, and as such no variance estimates exist other than those from a single dose study in normal healthy volunteers (P001). In order to provide an approximate estimate of power, the variability observed in P001 has been used for the power calculations presented below (Table 9). [redacted]

Table 9 Probability of Supporting Primary PD Hypothesis

Target GIRmax (mg/kg/min)	True GIRmax	Probability of Supporting Hypothesis
(1.5, 4.5)	1	2%
	1.5	30%
	2	86%
	2.5	99%
	3	99%
	3.5	99%
	4	86%
	4.5	30%
	5	2%
The calculations above were based [redacted] and N=6 per dose, and a posterior probability threshold of 70%.		

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-5160, 20.0 mg/mL	Sterile Solution for IV Administration, 1.0 mL per vial	Supplied by Sponsor

All supplies indicated in Table 10 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 10 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label vials. No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/IEC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to

the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

1. Heise et al. Expert Opin. Drug Metab. Toxicol 2015, 11:1193-1201.
2. Sinha VP et al DOM 2013, 16: 344-350
3. Bergenstal RM et al DOM 2016, 18: 1081-1088
4. Blevins T et al DOM 2016, 18: 1072-1080
5. Rizza RA, Mandarino LJ, Gerich JE. Dose-response characteristics for effects of insulin on production and utilization of glucose in man. Am. J. Physiol. 1981; 193: E630-639.
6. Argoud GM, Schade DS, Eaton RP. Underestimation of hepatic glucose production by radioactive and stable tracers. Am. J. Physiol. 1987; 252: E606-615.
7. Henry RR, Mudaliar S, Ciaraldi TP, Armstrong DA, Burke P, Pettus J, Garhyan P, Choi SL, Jacober SJ, Knadler MP, Lam ECQ, Prince MJ, Bose N, Porksen N, Sinha VP, Linnebjerg H. Basal insulin peglispro demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy subjects. Diabetes Care 2014; 37: 2609-2615.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.4 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD .

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

MK-5160 Subcutaneous	Pre-trial	Treatment Period	Post-trial	Total Collections	mL Per Collection	Total mL/ Test
Laboratory safety tests	1	5	1	7	10	70
FSH (if applicable) [a]	1			1	2	2
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	5	5
Blood for NEFA	0	14		14	2	28
Blood for glycerol	0	14		14	2	28
Plasma Ketones	0	12		12	2	24
Blood for Glucagon	0	5		5	2	10
Serum C-peptide only	1			1	2	2
Blood for triglycerides (only)	1	3		4	3.5	14
Blood for Anti-MK-5160 Antibody/Immunogenicity Assay	1		2	3	6	18
Blood for Anti-glargine (insulin) Antibody/Immunogenicity	1		2	3	6	18
Blood for Genetic Analysis		1		1	8.5	8.5
Blood for MK-5160/glargine PK Assay	0	40	1	41	6	246
					Total Blood Volume Per Subject [b]	473.5 mL

[a] For postmenopausal females without menses for at least 1 year.

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note that males have a Total Blood Volume of 471.5 mL.

12.4 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria[a]	**Potentially Significant Post-Randomization Findings (clarification on action to take)[b]**
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥ 25 bpm from baseline
Sinus Bradycardia	< 40 bpm	HR < 40 bpm and HR decrease of ≥ 5 bpm from baseline
Sinus Pause/Arrest	> 2.0 seconds	> 2.0 seconds
Atrial premature complex	> 1 beat	≥ 3 beats
Ventricular premature complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR < 40 bpm	Junctional Rhythm with HR < 40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB with Left Anterior Hemiblock (LAHB)	New onset LAHB
Right Axis Deviation	RBBB with Left Posterior Hemiblock (LPHB)	New onset LPHB
CONDUCTION		
1st degree A-V Block	PR ≥ 230 ms	PR ≥ 230 ms + increase of > 15 ms; or PR increase of > 25%
2nd degree A-V Block	Mobitz Type II	Mobitz Type II
3rd degree A-V Block	All	All
LBBB	All	All
RBBB	RBBB with LAHB/LPHB as defined above	New onset RBBB (not including intermittent or rate-related)
Incomplete Right BBB (ICRBBB) (QRS<120 ms)	No exclusion	Nothing
Short PR/ Preexcitation syndrome	Delta wave + PR <120 ms	Delta wave + PR <120 ms
Other Intra-ventricular Conduction Delay	QRS ≥ 130 ms	QRS ≥ 130 ms + increase of ≥ 10 ms
QTc (B or F)		
Male	QTc ≥ 450 ms	QTc ≥ 500 ms or increase of ≥ 60 ms from baseline
Female	QTc ≥ 450 ms	QTc ≥ 500 ms or increase of ≥ 60 ms from baseline
HYPERTROPHY		
Atrial abnormalities	Definite evidence of P mitrale or P pulmonale	Definite evidence of P mitrale or P pulmonale

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria[a]	**Potentially Significant Post-Randomization Findings (clarification on action to take)[b]**
Ventricular abnormalities	Voltage criteria for LVH plus Strain Pattern	Voltage criteria for LVH plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST elevation suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST depression suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T changes (In 2 or more leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All

Baseline is defined as Predose Day 1
ms=milliseconds, mm=millimeter
[a] Abnormalities noted, but not considered clinically significant should be discussed with Sponsor prior to dosing.
[b] Post-randomization assessments are at each specified timepoint. Discussion between the investigator and sponsor should occur if abnormalities are noted.

QTc Stopping Criteria:

1. Confirmed increase in absolute QTc ≥500 ms

If the QTc interval is ≥500 msec, the Sponsor should be notified and the ECGs should be reviewed by a cardiologist. The subject should be telemetry-monitored (until the QTc is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (e.g., a Cardiac or Intensive Care Unit) is available.

2. Confirmed increase in QTc from baseline of ≥60 ms

During each treatment period, if a subject demonstrates an increase in QTc interval ≥60 msec compared with mean predose baseline measurement, the ECG will be repeated twice within 5 minutes. The mean value of the QTc interval from the 3 ECGs will represent the value at that time point. If the average QTc interval increase from baseline for any postdose time point is ≥60 msec, the subject will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

12.5 Algorithm for Assessing Out-of-Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or pre-dose evaluation:

A. If all protocol-specified laboratory values are normal, the subject may enter the study.

B. If a protocol-specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the subject will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The subject may be excluded from the study;
   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
   3. The subject may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (e.g., elevated eosinophil count in a subject with asthma or seasonal allergies) the medical condition should be annotated on the laboratory report or
   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).
      a. If the repeat test value is within the normal range, the subject may enter the study.
      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential subject with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the subject may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the subject will be excluded from the study.

12.6 Criteria for Classifying Documented Episodes of Hyper- or Hypoglycemia as Adverse Events

The following will be used to determine adverse event (AE) reporting in cases of hypoglycemia and hyperglycemia:

Hypoglycemia is defined as glucose values ≤70 with symptoms and glucose values ≤50 with or without symptoms.

- If there are symptoms associated with low glucose (≤70), this is a **clinical** AE with a diagnosis of hypoglycemia.

- If there are no symptoms associated with a low glucose (>50 ≤70) it is up to the investigator to decide if this is a **laboratory** AE. The AE would be decreased glucose, not hypoglycemia.

- All glucose values ≤70 will require a comment that states whether or not there were associated symptoms of hypoglycemia.

Hyperglycemia:

If there are symptoms associated with a high glucose, this is a **clinical AE with a diagnosis of hyperglycemia.**

- Fingerstick glucose assessment can be performed at any time, at the discretion of the Investigator.

Correction of hyper-/hypoglycemia should be initiated as appropriate, at the discretion of the Investigator according to the site's standard operating procedures. Corrective actions for hypoglycemia include, but are not limited to: offering food/drink, IV dextrose bolus, and initiating or increasing the rate of a running IV dextrose infusion. Corrective actions for hyperglycemia include, but are not limited to: bolus SC injection of short-acting insulin, initiation or increase in the rate of a SC infusion of short-acting insulin, and initiation or increase in the rate of an IV infusion of insulin. The dose and/or frequency of MK-5160/glargine should not be changed for hyperglycemia.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	