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| Official Protocol Title: | A Single Ascending Dose Clinical Trial to Study the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MK-1092 in Healthy Subjects, Subjects with Type 1 Diabetes Mellitus, and Subjects with Type 2 Diabetes Mellitus |
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TITLE:

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

| Section Number (s) | Section Title(s) | Description of Change (s) | Rationale |
|-----------------------|---|--|---|
| 12.3; 7.1.5.5; | Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types; Trial Design/Dosing/ Procedures Modifications Permitted within Protocol Parameters; | Additional blood volume allowed for unscheduled pharmacokinetic (PK)/ pharmacodynamic (PD) or safety evaluations, including unscheduled Yellow Springs Instrument (YSI) blood glucose assessments during the clamp procedure, is increased from 50 mL to 100 mL for subjects participating in Part 4 only. This is completely offset by reductions in blood sampling for scheduled PK and PD evaluations in Part 4, Period 3. | Subjects in Part 4 participate in up to 3 clamp procedures (1 per study period). Due to an unexpectedly high rate of GlucoScout sensor failure during Part 4, frequent unscheduled YSI blood glucose assessments, as allowed per protocol, have been required to maintain subject safety during the clamp. Allowance of up to 100 mL of additional blood for safety/PK/PD assessments will include any unscheduled YSI glucose assessments during the subject's participation in the study. |

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

| Section Number (s) | Section Title (s) | Description of Change (s) | Rationale |
|-----------------------------|--|--|---|
| 6.4; 12.3 | Trial Flow Chart – Part 4; Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types; | <p>The following time points for MK-1092/ glargine PK evaluations were removed from the sampling scheme for Part 4 Period 3 only: 30 min, 2 hr, and 96 hr post-dose. The revised sampling scheme is noted in footnote ‘m’ of the flowchart.</p> <p>The following time points for NEFA, glycerol, C-peptide and ketone PD evaluations were removed from the sampling scheme for Part 4 Period 3 only, as applicable: 2 hr, 6 hr, 12 hr, and 36 hr post-dose. The revised sampling scheme is noted in a new footnote ‘x’ of the flowchart.</p> | <p>The reduction in blood collections for PK/PD will offset the increase in allowable blood that may be collected for unscheduled safety assessments of up to 100 mL for subjects in Part 4. The reduction in PK/PD sampling for this period will not significantly impact the ability to achieve the study objectives related to these end points.</p> |
| 1.0; 2.2; 5.3 | Trial Summary; Trial Diagram; Randomization or Treatment Allocation | <p>Clarified dose for Part 4 Period 2 to MK-1092 16 nmol/kg or glargine 3.0 nmol/kg.</p> | <p>Dose decision following review of available safety, PK and PD data as per Section 5.2.1.2 Dose Modification (Escalation/Titration/Other).</p> |

| Section Number (s) | Section Title (s) | Description of Change (s) | Rationale |
|--------------------|--|---|-------------------------|
| 2.1; 4.1.2 | Trial Design; Ongoing Clinical Trials | Clarified current enrollment status and doses selected for completed panels/periods in Parts 1 – 4 at the time of protocol amendment 001-04. | Text added for clarity. |
| 4.1.2 | Ongoing Clinical Trials | Updated safety summary to include all injection site reactions and rash events in P001 reported at the time of protocol amendment 001-04. | Text added for clarity. |
| 4.1.2; 4.2.3.1 | Ongoing Clinical Trials; Safety Endpoints | Updated summary of the observed PK, GIR_{max} and ADA/AIA results to include available data from completed panels or periods of Parts 1 – 4 at the time of protocol amendment 001-04. | Text added for clarity. |

1.0 TRIAL SUMMARY

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|-----------------------------|---|
| Abbreviated Title | Single Ascending Dose Study of MK-1092 in Healthy Subjects, Subjects with Type 1 Diabetes Mellitus, and Subjects with Type 2 Diabetes Mellitus |
| Sponsor Product Identifiers | MK-1092 |
| 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 (Part 1, Part 3, Part 4) and Open-Label (Part 2) |
| Treatment Groups | <p><u>Part 1 (6 on MK-1092; 2 on glargine per panel)</u> Panel A: MK-1092 4.0 nmol/kg or glargine 3.0 nmol/kg Panel B: MK-1092 8.0 nmol/kg or glargine 3.0 nmol/kg Panel C: MK-1092 16 nmol/kg or glargine 3.0 nmol/kg Panel D: MK-1092 32 nmol/kg or glargine 3.0 nmol/kg Panel E: MK-1092 64 nmol/kg or glargine 3.0 nmol/kg Gender/Age: Healthy males and females (of non-child bearing potential), 18-50 years (inclusive)</p> <p><u>Part 2 (4 on MK-1092 + Humalog[®])</u> Panel F: MK-1092 (8.0 nmol/kg as based on Part 1) + Humalog[®] 1.2 nmol/kg Gender/Age: Healthy males and females (of non-child bearing potential), 18-50 years (inclusive)</p> <p><u>Part 3 (6 on MK-1092; 2 on glargine per panel)</u> Panel G: MK-1092 (8.0 nmol/kg as based on Part 1) or glargine 3.0 nmol/kg Panel H: MK-1092 (32 nmol/kg) or glargine 3.0 nmol/kg Panel I: MK-1092 (\leq 64 nmol/kg) or glargine 3.0 nmol/kg* Panel J: MK-1092 (\leq 64 nmol/kg) or glargine 3.0 nmol/kg Gender/Age: Male and female subjects (of non-child bearing potential) with T1DM, 18-60 years (inclusive)</p> <p>*Per PCL#10, Panel I will be omitted.</p> <p><u>Part 4 (6 on MK-1092; 3 on glargine)</u> Period 1: MK-1092 (32 nmol/kg as based on Part 1) or glargine 3.0 nmol/kg Period 2: MK-1092 (16 nmol/kg) or glargine 3.0 nmol/kg Period 3: MK-1092 (\leq 64 nmol/kg) or glargine 3.0 nmol/kg Gender/Age: Male and female subjects (of non-child bearing potential) with T2DM, 18-60 years (inclusive)</p> |
| Number of trial subjects | Approximately 77 subjects will be enrolled. |
| Estimated duration of trial | The Sponsor estimates that the trial will require approximately 15 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. |

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| Duration of Participation | <p>Each subject in Parts 1, 2 and 3 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 screening phase of approximately 2-4 weeks each subject will be receiving assigned treatment for approximately 1 day. After the end of treatment each subject will be followed for 4 weeks.</p> <p>Each subject in Part 4 will participate in the trial for approximately 14-16 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of approximately 2-4 weeks each subject will be receiving assigned treatment for approximately 1 day in each period followed by a minimum 7 day washout between doses. After the end of the final treatment each subject will be followed for 4 weeks.</p> |
| Randomization Ratio | <p>Part 1 (MK-1092 / glargine): 3:1; Part 2 (MK-1092 only); Part 3 (MK-1092 / glargine): 3:1; Part 4 (MK-1092 / glargine): 6:3</p> |

2.0 TRIAL DESIGN

2.1 Trial Design

This is an active- and placebo-controlled, single-site, four-part trial of MK-1092 in healthy adult subjects, in subjects with type 1 diabetes mellitus (T1DM), and in subjects with type 2 diabetes mellitus (T2DM) to be conducted in conformance with Good Clinical Practices.

This is the first-in-human study for MK-1092, an insulin receptor partial agonist (IRPA), being developed as a basal insulin for patients with both type 1 (T1DM) and type 2 (T2DM) diabetes mellitus. All subjects will undergo a euglycemic clamp during and after subcutaneous (SC) administration of MK-1092, with or without infusion of lispro (Humalog®), or glargine. The purpose of the study is to determine safety and tolerability of MK-1092 in healthy adult subjects, in adult subjects with T1DM, and in adult subjects with T2DM relative to glargine, to obtain pharmacokinetics (PK) of MK-1092 administered SC, and to determine the maximal glucose infusion rate (GIR_{max}) required to maintain target glucose levels in the euglycemic setting following SC dosing of MK-1092.

There will be four parts in this study. In Part 1, healthy adult subjects will be randomized to receive MK-1092 SC or glargine SC, as a single dose under the euglycemic clamp. Subjects will be blinded in a double-dummy fashion, so that each subject will receive MK-1092/glargine and a matched placebo to the alternative active treatment. Part 1 will employ sentinel dosing. The first three (3) subjects enrolled in each panel of Part 1 will be dosed individually with the trial treatment for which they were randomly allocated as per the computer generated allocation schedule (MK-1092 or glargine). Subsequent subjects will not be dosed until at least 24 hours have elapsed after dosing of each of the first three subjects in each panel of Part 1. The starting dose in Part 1 Panel A is 4.0 nmol/kg. Dosing in all subsequent panels of Part 1 will commence upon review of the safety data from previous panels within Part 1 and determination of an acceptable safety profile to continue dose escalation. Up to 5 doses of MK-1092 will be administered in successive panels. The glargine dose will be the same in all panels of Part 1 and is expected to achieve GIR_{max} .

~2 mg/kg/min. The MK-1092 doses will include, and could potentially escalate beyond, the expected therapeutic insulin concentration range leading to a GIR_{max} ~1-2 mg/kg/min. Different subjects will participate in each panel (N=6/panel receiving MK-1092, N=2/panel receiving glargine). The objectives for this part will assess safety and tolerability of the SC injection, PK, and PD endpoints for MK-1092 and glargine in healthy adult subjects. Once a safe and tolerated dose that achieves GIR_{max} ~1-2 mg/kg/min is identified in Part 1, Part 2 will start and subsequent panels in Part 1 will be paused. Completion of Part 1 will be dependent upon the need for further dose exploration in healthy adult subjects.

At the time of protocol amendment 02, a dose of 8.0 nmol/kg was safe, well-tolerated and had achieved GIR_{max} ~ 1-2 mg/kg/min. This dose was then tested in Part 2, and subsequent panels of healthy adult subjects were resumed. At the time of protocol amendment 03, the maximum dose tested to date is 64 nmol/kg in Part 1 Panel E. Data review for the 64 nmol/kg dose is ongoing. The preliminary review of Panel E indicates that the 64 nmol/kg dose, like the doses in Panels A-D (4 - 32 nmol/kg) has been safe and well-tolerated.

In Part 2, four different healthy adult subjects than participated in Part 1 will be enrolled in a single panel and receive MK-1092 SC as a single dose under the euglycemic clamp; all subjects in this part will also receive an IV infusion of Humalog for three hours, starting ~12 hr after SC administration of MK-1092, a time at which MK-1092 is anticipated to have a glycemic effect. The actual start time of Humalog infusion may be altered based on data from Part 1 and will be communicated to the site by a Protocol Clarification Letter prior to dosing.

At the time of protocol amendment 02, the MK-1092 dose that was administered in Part 2 Panel F had been selected following review of data from Part 1 as the dose that achieves a GIR_{max} of ~1-2 mg/kg/min (8.0 nmol/kg) and had been communicated to the site by a Protocol Clarification Letter prior to dosing. The purpose of Part 2 was to assure that a high dose of Humalog infusion could adequately reduce hyperglycemia in individuals who have received a therapeutic dose of MK-1092, as defined by achieving a GIR_{max} > 4 mg/kg/min during Humalog infusion. This part was open-label as all subjects were assigned to a single treatment by non-random assignment. The objectives for this part are exploratory and will assess safety, tolerability, and adequate glycemic effect of IV Humalog after SC administration of MK-1092 in healthy adult subjects.

In Part 3, adult subjects with T1DM will be randomized to receive MK-1092 SC or glargine SC, as a single dose under the euglycemic clamp. Subjects will be blinded in a double-dummy fashion, so that each subject will receive MK-1092/glargine and a matched placebo to the alternative active treatment. Dosing in the first panel of this part will use a SC dose no higher than one that has been determined to be safe, tolerated, and has achieved GIR_{max} of ~1-2 mg/kg/min in healthy adult subjects in Part 1 and has been tested with Humalog infusion in Part 2 in healthy adult subjects. At the time of protocol amendment 03, a dose of 8.0 nmol/kg had fulfilled these criteria and was safe and well-tolerated as the first dose in Panel G. At the time of amendment 03, Part 3 Panel H (32 nmol/kg or glargine) was ongoing.

Dosing in all subsequent panels of Part 3 will commence upon review of the safety data from previous panels within Part 3 and determination of an acceptable safety profile to continue dose escalation. Up to 3 doses of MK-1092 will be administered in successive panels. The glargine dose will be the same in all panels of Part 3 and is expected to achieve $GIR_{max} \sim 2$ mg/kg/min. The MK-1092 doses will include, and may escalate beyond, the expected therapeutic insulin concentration range for a GIR_{max} of $\sim 1-2$ mg/kg/min. Doses in Part 3 will not exceed 64 nmol/kg SC, which is the highest planned dose in the clinical program. Different subjects will participate in each panel (N=6/panel receiving MK-1092, N=2/panel receiving glargine). The objectives for this part will assess safety and tolerability of the SC injection, PK, and PD endpoints for MK-1092 and glargine in adult subjects with T1DM.

Originally up to 4 doses of MK-1092 were planned for Part 3. However, per PCL #10 (dated 21-Mar-2018), Part 3 Panel I will not be conducted as it is anticipated that no more than 3 doses in Part 3 will be needed to assess the safety, PK and PD in subjects with T1DM, following review of data from Part 1. Additionally, an operational pause has been added between Panel H and Panel J in Part 3 only. The decision of whether to initiate Panel J will be made after thorough review of all available data from Panels G and H.

In Part 4, adult subjects with T2DM will be randomized to receive MK-1092 SC or glargine SC, as a single dose under the euglycemic clamp. Adult subjects with T2DM may use insulin as part of the pre-study regimen (*i.e.*, insulin-requiring T2DM) or may not use insulin as part of the pre-study regimen (*i.e.*, non-insulin-requiring T2DM).

In Part 4, subjects will be blinded in a double-dummy fashion, so that each subject will receive MK-1092/glargine and a matched placebo to the alternative active treatment. Dosing in the first period of this part will use a SC dose no higher than one that has been determined to be safe and tolerated in Part 1. At the time of protocol amendment 03, doses ≤ 64 nmol/kg have fulfilled these criteria. At the time of protocol amendment 04, a dose of 32 nmol/kg was administered in Period 1 and a dose of 16 nmol/kg was administered in Period 2. Dosing in Period 3 of Part 4 will commence upon review of the safety data from previous periods within Part 4 and determination of an acceptable safety profile to continue dose escalation. Up to 3 doses of MK-1092 will be administered in successive periods. The glargine dose will be the same in all periods of Part 4 and is expected to achieve $GIR_{max} \sim 2$ mg/kg/min. The MK-1092 doses will include, and may escalate beyond, the expected therapeutic insulin concentration range for a GIR_{max} of $\sim 1-2$ mg/kg/min. Doses in Part 4 will not exceed 64 nmol/kg SC, which is the highest planned dose in the clinical program. Unlike in Parts 1-3, in Part 4 the same subjects will participate in each period (N=6 receiving MK-1092, N=3 receiving glargine). Subjects in Part 4 who are randomized to MK-1092 in Period 1 will receive MK-1092 in the subsequent periods, and subjects in Part 4 who are randomized to glargine in Period 1 will receive glargine in the subsequent periods. All subjects will complete dosing in Period 1 prior to the start of Period 2, and all subjects will complete dosing in Period 2 prior to the start of Period 3. In addition, determination of an acceptable safety profile in Period 1 will be required prior to starting Period 2 and an acceptable safety profile in Period 2 will be required prior to starting Period 3. At least 7 days will occur between dose administrations in Part 4 to allow for washout. Furthermore, an operational pause will be implemented between Period 2 and Period 3 in Part 4 only to allow sufficient time for analysis of data collected in prior periods of Part 4 and/or panels of Parts 1 and 3 to

inform on dose decisions related to Period 3. The objectives for this part will assess safety and tolerability of the SC injection, PK, and PD endpoints for MK-1092 and glargine in adult subjects with T2DM.

Activities prior to and following the euglycemic clamp will differ for healthy adult subjects and for adult subjects with T1DM or T2DM. Healthy adult subjects (Part 1 and 2) will be admitted to the clinical research unit (CRU) on Day -1 and will fast for at least 8 h prior to the start of the euglycemic clamp and for the duration of the clamp. Healthy adult subjects will be discharged approximately 48 hrs after the start of the euglycemic clamp.

Adult subjects with T1DM (Part 3) will be admitted to the CRU on Day -4, placed on continuous glucose monitoring (CGM), and started on a SC insulin pump to maintain glycemic control with an appropriate regimen of basal and bolus insulin during washout of pre-study insulin therapy.

Adult subjects with T2DM (Part 4) will be admitted to the CRU on Day -4 of each period and placed on CGM. For all subjects with insulin-requiring T2DM, a SC insulin pump will be started to maintain glycemic control with an appropriate regimen of basal and bolus insulin. Subjects with non-insulin-requiring T2DM will not be placed on SC insulin pump unless the investigator determines this to be necessary to maintain glycemic control during the admission.

Subjects who are already using a SC insulin pump for treatment of T1DM or T2DM may continue to use their own SC pump during the study at the discretion of the investigator; however the investigator may alter the basal and bolus settings or require the use of a site-provided SC insulin pump based on medical judgment. The insulin pump (if required) and CGM may remain in place until discharge or be removed based on the clinical judgement and discretion of the investigator. Insulin, if required, will be administered via the insulin pump throughout the trial, except during the clamp, according to standard clinical practice and at the discretion of the investigator. Subjects will have glucose assessments by fingerstick and/or CGM before meals, prior to bedtime, at least once overnight, and as needed per the subject and/or the investigator.

In the evening on Day -1 adult subjects with T1DM and T2DM will begin a fast lasting at least 8 hours prior to the start of a euglycemic clamp. During the fast, the basal insulin rate on SC pump (if active) will be suspended, and subjects will receive IV insulin and IV dextrose, as needed, to set blood glucose levels at ~100 mg/dL prior to dosing and clamp initiation. After dosing, the insulin infusion will be weaned as appropriate to maintain glucose concentrations at ~100 mg/dL. Once the insulin infusion is weaned off, a variable rate glucose infusion will be initiated and titrated to maintain blood glucose close to target. Subjects will remain fasted for the duration of the clamp. After completion of the euglycemic clamp, adult subjects with T1DM and T2DM will eat and resume their pre-study anti-diabetic regimen; however, they will continue to wear the CGM and use the insulin pump as needed until glycemic control has been re-established using the pre-study therapy. Subjects will be discharged from the site ~48 hours after the start of the clamp. The time of discharge may be dependent upon glycemic control being re-established after the euglycemic clamp and can be lengthened based on investigator discretion.

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-1092 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 design is depicted in [Figure 1](#), [Figure 2](#) and [Table 1](#). Subjects participating in Parts 1, 3, and 4 will receive injections of MK-1092/glargine and placebo matched to the alternative active treatment. Subjects in Part 2 will receive open label SC MK-1092 and IV Humalog.

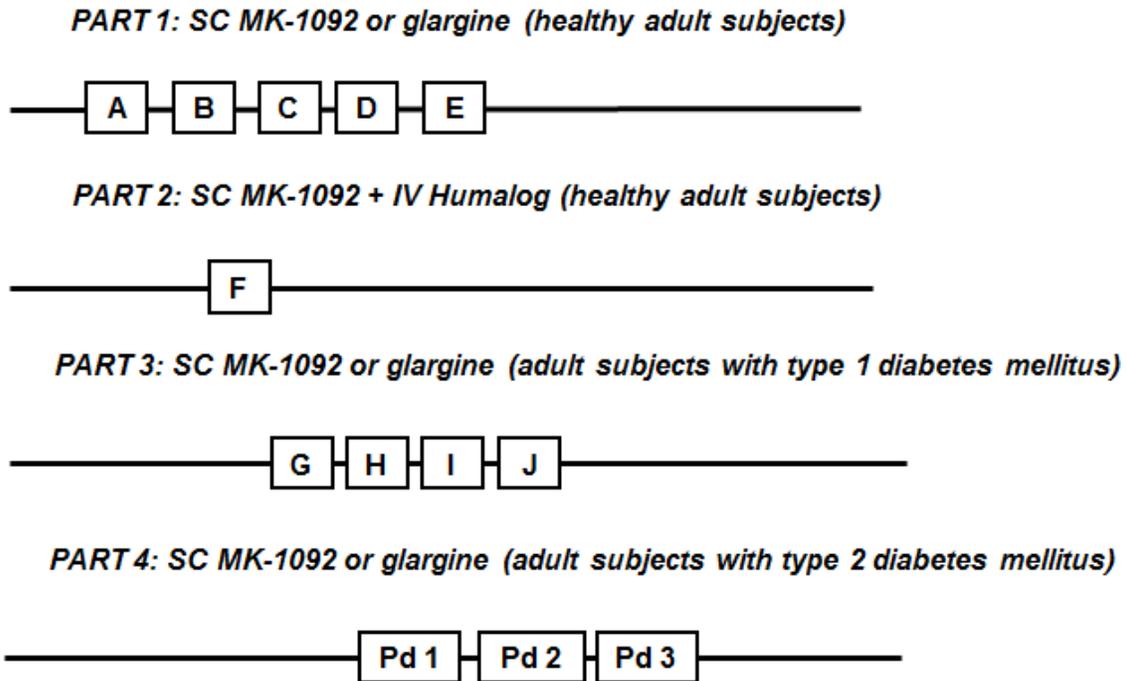
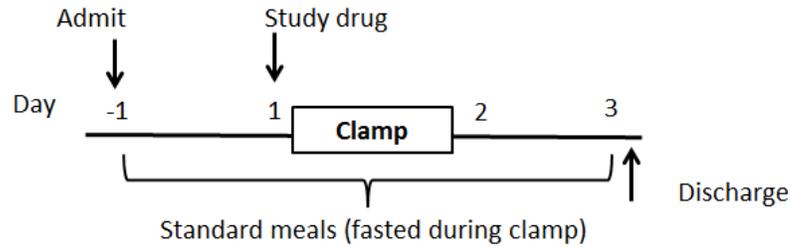


Figure 1 Overall Trial Design

*Per PCL#10 Panel I will be omitted.

Parts 1 and 2 (healthy adult subjects)



Parts 3 and 4 (adult subjects with T1DM and T2DM, respectively)

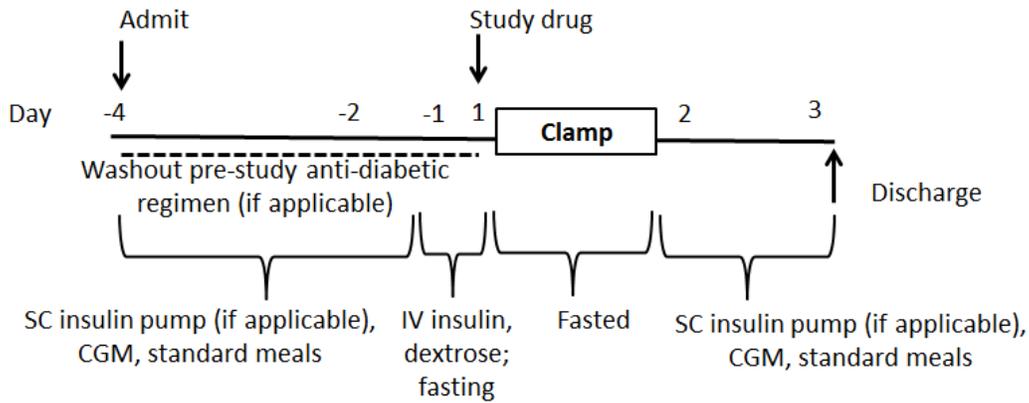


Figure 2 Study Design

*In Parts 1-3 subjects will participate in only one panel. In Part 4, each subject will participate in up to 3 periods. Each period in Part 4 will follow the study design above.

Table 1 Trial Diagram

| | | | | | |
|--|---|---|--|--|--|
| Part 1 ^{a,b} (SC MK-1092 or glargine) | Panel A | Panel B | Panel C | Panel D | Panel E |
| | Glargine (3.0 nmol/kg ^c) or MK-1092 (4.0 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (8.0 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (16 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (32 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (64 nmol/kg) |
| Part 2 ^{a,d} (SC MK-1092 + IV Humalog) | Panel F | | | | |
| | MK-1092 (8.0 nmol/kg based on Part 1) + Humalog 1.2 nmol/kg ^e | | | | |
| Part 3 ^{a,f} (SC MK-1092 or glargine) | Panel G | Panel H | Panel I^g | Panel J | |
| | Glargine (3.0 nmol/kg ^c) or MK-1092 (8.0 nmol/kg based on Part 1) | Glargine (3.0 nmol/kg ^c) or MK-1092 (32 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (≤ 64 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (≤ 64 nmol/kg) | |
| Part 4 ^{a,f} (SC MK-1092 or glargine) | Period 1 | Period 2 | Period 3 | | |
| | Glargine (3.0 nmol/kg ^c) or MK-1092 (32 nmol/kg based on Part 1) | Glargine (3.0 nmol/kg ^c) or MK-1092 (16 nmol/kg) | Glargine (3.0 nmol/kg ^c) or MK-1092 (≤ 64 nmol/kg) | | |

SC – subcutaneous; IV – intravenous

^a The suggested doses may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous parts, panels, or periods.

^b In Part 1, healthy adult subjects will be randomized to receive MK-1092 or glargine within each panel, with two subjects receiving glargine and six receiving MK-1092 according to a computer-generated allocation schedule. In addition to MK-1092 or glargine, subjects will also receive placebo (i.e., subjects receiving MK-1092 will also receive placebo matched to glargine, and subjects receiving glargine will also receive placebo matched to MK-1092). Approximate injection volumes for doses of MK-1092 are: 2.4 μL/kg for 4.0 nmol/kg, 4.7 μL/kg for 8.0 nmol/kg, 9.4 μL/kg for 16 nmol/kg, 19 μL/kg for 32 nmol/kg, 38 μL/kg for 64 nmol/kg.

^c Unit conversions for glargine dosing: 3.0 nmol/kg = 0.5 U/kg. Injection volume for glargine 3.0 nmol/kg = 5 μL/kg.

^d In Part 2, four healthy adult subjects will receive MK-1092 within a single panel. The dose of MK-1092 in Part 2 is the SC dose that leads to a GIR_{max} of ~1-2 mg/kg/min, based on the results of Part 1, and will not exceed 64 nmol/kg.

^e Unit conversions for Humalog dosing: 1.2 nmol/kg = 0.2 U/kg

^f In Part 3, adult subjects with type 1 diabetes mellitus will be randomized to receive MK-1092 or glargine within each panel, with two subjects receiving glargine and six receiving MK-1092 according to a computer-generated allocation schedule. In Part 4, adult subjects with type 2 diabetes mellitus will be randomized to receive MK-1092 or glargine within each period, with the same three subjects receiving glargine in each period and the same six subjects receiving MK-1092 in each period according to a computer-generated allocation schedule. In addition to MK-1092 or glargine, subjects in Parts 3 and 4 will also receive placebo (i.e., subjects receiving MK-1092 will also receive placebo matched to glargine, and subjects receiving glargine will also receive placebo matched to MK-1092). The dose of MK-1092 in Part 3 Panel G (8 nmol/kg) is no higher than the SC dose that leads to a GIR_{max} of ~1-2 mg/kg/min in healthy adult subjects, based on the results of Part 1, and has been tested in healthy adult subjects with Humalog infusion in Part 2. The dose of MK-1092 in Part 4 Period 1 (32 nmol/kg) is no higher than one that has been determined to be safe and tolerated in Part 1. The maximum dose tested in Part 3 and Part 4 will not exceed 64 nmol/kg.

^g Per PCL#10 Panel I will be omitted.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

- 1) **Objective:** To evaluate the safety and tolerability of single SC doses of MK-1092 in healthy adult subjects. (Parts 1 and 2)
- 2) **Objective:** To evaluate the safety and tolerability of single SC doses of MK-1092 in adult subjects with T1DM and in adult subjects with T2DM. (Part 3 and Part 4)
- 3) **Objective:** To determine the mean GIR_{max} required to maintain target glucose levels in a euglycemic clamp setting of MK-1092 in adult subjects with T1DM following single SC dosing. (Part 3)

Hypothesis:

- 1) At a dose with sufficient safety, the mean GIR_{max} after single SC administration of MK-1092 in adult subjects with T1DM is between 1.5 and 4.5 mg/kg/min. (Part 3)

3.2 Secondary Objective(s) & Hypothesis(es)

- 1) **Objective:** To determine the mean GIR_{max} required to maintain target glucose levels in a euglycemic clamp setting of MK-1092 in healthy adult subjects following single SC dosing. (Part 1)
- 2) **Objective:** To determine the mean GIR_{max} required to maintain target glucose levels in a euglycemic clamp setting of MK-1092 in adult subjects with T2DM following single SC dosing. (Part 4)
- 3) **Objective:** To determine the mean of the time-weighted average based on GIR [TWA(GIR)] required to maintain target glucose levels in a euglycemic clamp setting of MK-1092 in healthy adult subjects, in adult subjects with T1DM, and in adult subjects with T2DM following single SC dosing. (Parts 1, 3, and 4)
- 4) **Objective:** To estimate the plasma PK profile (e.g., C_{max} , $AUC_{0-\infty}$, CL/F , T_{max} , apparent terminal $t_{1/2}$) of MK-1092 after SC dosing in healthy adult subjects, in adult subjects with T1DM, and in adult subjects with T2DM. (Parts 1, 3, and 4)

3.3 Exploratory Objectives

- 1) **Objective:** To explore the levels of serum free fatty acids (non-esterified fatty acids, NEFA) and plasma glycerol after SC dosing of MK-1092 or glargine in healthy adult subjects, in adult subjects with T1DM, and in adult subjects with T2DM. (Parts 1, 2, 3, 4)
- 2) **Objective:** To explore the PK and glycemic effect of addition of IV Humalog infusion following SC dosing of MK-1092 in healthy adult subjects. (Part 2)
- 3) **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-1092.

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 [1]. 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 [2]. According to CDC statistics, 14% of all patients with diabetes in the U.S. are on insulin alone, and another 13% are on a combination of insulin and oral therapy [2]. Basal insulin, which is intended to maintain normal glucose levels during fasting, is the most commonly used form of insulin by patients with T2DM and is used by all patients with T1DM.

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 thus often settle at moderate under-dosing of basal insulin and/or preemptive ingestion of carbohydrates, such as snacking before exercise or bedtime, to mitigate the risk for hypoglycemia associated with basal insulin. However, these strategies occur 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 basal insulins, thus allowing more confidence for practitioners and patients to dose titrate IRPA to attain target goals for control of fasting glucose.

MK-1092 lowers glucose levels effectively but with a flatter dose response curve, an attenuated maximal effect, and extended duration of action in diabetic animal models relative to comparator insulins.

This study will be the first introduction of MK-1092 into human subjects, and will evaluate the safety, tolerability, PK and PD of MK-1092 in healthy adult subjects, adult subjects with T1DM, and adult subjects with T2DM.

4.1.2 Ongoing Clinical Trials

Preliminary Safety and Tolerability

To date, single subcutaneous doses of MK-1092 up to 64 nmol/kg have been evaluated in Part 1 (healthy adult subjects: Panels A [4.0 nmol/kg], B [8.0 nmol/kg], C [16 nmol/kg], D

[32 nmol/kg], and E [64 nmol/kg]); a dose of 8.0 nmol/kg has been evaluated during co-administration with IV Humalog in Part 2 (healthy adult subjects); doses of 8.0 nmol/kg (Panel G) and 32 nmol/kg (Panel H) have been evaluated in Part 3 (subjects with T1DM), and doses of 32 nmol/kg (Period 1) and 16 nmol/kg (Period 2) have been evaluated in Part 4 (subjects with T2DM).

All doses have been safe and well-tolerated. There have been no serious adverse events and no discontinuations due to treatment-emergent adverse events. All adverse events have been mild or moderate and have resolved spontaneously.

There have been no clinically significant changes in vital signs, laboratory parameters, or ECG findings. In Part 1 Panel B (8.0 nmol/kg), three different subjects experienced a mild and transient injection site reaction (injection site pain, injection site pain, injection site tenderness, respectively). In Part 1 Panel C (16 nmol/kg), three different subjects experienced a mild and transient injection site reaction (injection site pain, injection site pain, injection site burning, respectively). In Part 1 Panel E (64 nmol/kg), one subject experienced a mild and transient injection site soreness. In Part 3 Panel H (32 nmol/kg), one subject experienced a mild and transient injection site tenderness. In Part 4 Period 1 (32 nmol/kg), one subject experienced mild and transient pain at the injection site and another subject experienced an upper chest rash due to ECG leads. None of these events were evaluated as being an event of clinical interest (ECI). In Part 3 Panel G (8 nmol/kg), one subject experienced a mild and transient injection site erythema that was reported to the Sponsor as an ECI as well as a separate experience of transient erythema to ECG leads. One other subject in Part 2 Panel F reported an ECI of dermatitis that was deemed unrelated to the study drug by the investigator. No injection site reactions were reported in other panels, including Part 1 Panel A (4 nmol/kg) and Panel D (32 nmol/kg). Treatment allocation (MK-1092 vs glargine) for Part 1, Part 3, and Part 4 remains blinded.

Preliminary Pharmacokinetics

A summary of the observed PK for the MK-1092 4.0 nmol/kg to 64 nmol/kg dose groups in Part 1 and for Part 3 Panel G (8.0 nmol/kg) is provided below. The PK from Part 3 Panel H and from Part 4 (Periods 1 and 2) is pending at the time of amendment 04.

| Preliminary PK Parameters for MK-1092-001 Part 1 (4.0 – 64 nmol/kg) and Part 3 (8.0 nmol/kg) | | | | | | |
|---|-----------------------|---|-----------------------------|-----------------------------|----------------------------------|-------------------------------------|
| | Dose (nmol/kg) | T_{max} (hr)[¶] | t_{1/2} (hr) | C_{max} (nM) | AUC_{0-∞} (nM·hr) | AUC_{0-24hr} (nM·hr) |
| Part 1 | 4.0 | 18 (9.0-18) | 7.00 (31.42) | 0.382 (21.70) | 9.86 (15.37) | 6.43 (20.78) |
| | 8.0 | 12 (4.0-18) | 6.37 (25.85) | 0.747 (25.03) | 17.8 (15.36) | 12.94 (22.49) |
| | 16 | 18 (4.0-24) | 5.47 (27.90) | 1.63 (12.68) | 37.8 (10.09) | 26.03 (21.43) |
| | 32 | 18 (9.0-18) | 5.79 (16.91) | 2.91 (18.73) | 75.8 (10.28) | 48.86 (15.83) |
| | 64 | 12 (12-18) | 9.03 (73.0) | 6.82 (27.6) | 161 (14.1) | 108 (27.1) |
| Part 3 | 8.0 | 15 (9.0-18) | 7.81 (21.6) | 0.788 (20.4) | 22.6 (22.4) | 13.9 (17.8) |
| [¶] Median (Min-Max). All other parameters are expressed as geometric mean (CV). | | | | | | |

Exposures were comparable to predicted values. Following a single dose administration, the geometric mean of apparent terminal half-life ranged ~5.5-9 hr and T_{max} ranged ~12-18 hr at 4.0 nmol/kg to 64 nmol/kg in Part 1. MK-1092 AUC_{0-∞} and C_{max} appeared to be approximately dose proportional. The PK parameters for 8.0 nmol/kg were similar in Part 1 and Part 2 based on preliminary analysis. The PK parameters at 8.0 nmol/kg in Part 3 were comparable to the PK parameters at 8.0 nmol/kg in Part 1.

No anti-drug antibodies (ADAs) or anti-insulin antibodies (AIA) have been detected in Part 1 Panel A-D, Part 2, or Part 3 at up to 28 days after dosing. In Part 1 Panel E, no ADA or AIA have been detected at up to 28 days in 7 of 8 subjects; the 8th subject was lost to follow-up after 14 days and no ADA and AIA had been detected at up to 14 days after dosing for this subject.

Preliminary Pharmacodynamics

A summary of the observed GIR_{max} for the MK-1092 4.0 nmol/kg to 64 nmol/kg dose groups in Part 1 (NHV), for the MK-1092 8.0 nmol/kg and 32 nmol/kg dose group in Part 3 (T1DM), and for the 32 nmol/kg and 16 nmol/kg dose group in Part 4 (T2DM) are provided below. The GIR_{max} for all adult subjects randomized to glargine in any group of Part 1 (Panels A – E), Part 3 (Panel G and H), and Part 4 (Period 1 and 2) are also provided.

| Part 1 GIR_{max} values for MK-1092-001 (4-64 nmol/kg) and Glargine (3.0 nmol/kg), Part 3 GIR_{max} values for MK-1092-001 (8.0 nmol/kg and 32 nmol/kg) and Glargine (3.0 nmol/kg), and Part 4 GIR_{max} values for MK-1092-001 (16 nmol/kg and 32 nmol/kg) and Glargine (3.0 nmol/kg) | | |
|---|---------------------------------|--------------------------------------|
| | Dose | GIR_{max} (mg/kg/min) |
| Part 1 | MK-1092 4.0 nmol/kg | 0.9 |
| | MK-1092 8.0 nmol/kg | 1.7 |
| | MK-1092 16 nmol/kg | 3.1 |
| | MK-1092 32 nmol/kg | 3.3 |
| | MK-1092 64 nmol/kg | 4.4 |
| | Glargine 3.0 nmol/kg (0.5 U/kg) | 2.9 |
| | Part 3 | MK-1092 8.0 nmol/kg |
| MK-1092 32 nmol/kg | | 2.9 |
| Glargine 3.0 nmol/kg (0.5 U/kg) | | 2.5 |
| Part 4 | MK-1092 16 nmol/kg | 1.4 |
| | MK-1092 32 nmol/kg | 1.9 |
| | Glargine 3.0 nmol/kg (0.5 U/kg) | 1.2 |

In Part 1, a dose of 8.0 nmol/kg was safe, well-tolerated, and achieved GIR_{max} of ~1-2 mg/kg/min in healthy adult subjects. Therefore, this dose was tested with Humalog infusion in Part 2 in healthy adult subjects. In Part 2, all healthy subjects achieved GIR_{max} > 4 mg/kg/min. A dose of MK-1092 8.0 nmol/kg was therefore used as the initial dose in Part 3 (adult subjects with T1DM). After 8.0 nmol/kg was tested in Part 2, subsequent panels in Part 1 testing up to 64 nmol/kg have been resumed. A dose of 32 nmol/kg was used as the initial dose in Part 4 (adult subjects with T2DM). A dose of 16 nmol/kg was used as the second dose in Part 4 so as to explore the PD effects of doses below 32 nmol/kg. These doses have been safe and well-tolerated.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

This study is being conducted to assess the initial clinical safety, tolerability, PK, and PD of MK-1092 following administration to humans. PK after SC administration will be assessed. PD will be assessed by measuring the glucose infusion rate (GIR) after administration of MK-1092 under euglycemic clamp conditions. In addition, the glycemic effect of Humalog infusion following SC MK-1092 administration will be assessed, also under euglycemic clamp conditions.

The study population is comprised of healthy male and female (women of non-child bearing potential, WONCBP) subjects, adult subjects with T1DM, and adult subjects with T2DM. In Parts 1 and 2 of the study, MK-1092 will be administered to healthy subjects to gain an initial understanding of the safety/tolerability, PK, and PD profile of MK-1092 prior to administration in adult subjects with T1DM and T2DM. Because the target population for MK-1092 includes patients with T1DM and T2DM, including adult subjects with T1DM and T2DM in this protocol will provide an early read-out of the therapeutic potential for MK-1092.

Adult subjects with T1DM and T2DM will not be administered MK-1092 until a safe and tolerated dose that achieves a GIR \sim 1-2 mg/kg/min (Part 1) and that has been tested with Humalog infusion (Part 2) in healthy adult subjects is identified. At the time of protocol amendment 03, a dose of 8.0 nmol/kg has fulfilled this requirement and was tested in Part 3 Panel G. Female subjects of child-bearing potential are not included in this study due to the limited assessment of MK-1092 on reproduction and development. At the time protocol amendment 03, approximately 77 subjects will participate in the study, including up to approximately 44 healthy male and female subjects (40 in Part 1, 4 in Part 2) in the age range of 18-50 years (inclusive), up to approximately 24 male and female adult subjects with T1DM (Part 3) in the age range of 18-60 years (inclusive), and up to approximately 9 male and female adult subjects with T2DM (Part 4) in the age range of 18-60 years (inclusive).

4.2.2 Rationale for Dose Selection/Regimen/Modification

As this is a Phase I assessment of MK-1092 in humans, and the pharmacokinetic, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 7.1.5.5 - Trial Design/Dosing/Procedures Modifications Permitted within Protocol Parameters.

As noted above, there are several objectives in this trial, extending beyond the standard goals of a FIH trial in understanding safety, tolerability, and PK. Specifically, the trial is designed to also examine PD of MK-1092 with respect to the short-term glycemic effect of MK-1092 across a range of doses in comparison to a single dose of glargine insulin, provide an assessment of the ability of MK-1092 to inhibit lipolysis, and test the glycemic effect of IV Humalog following SC administration of MK-1092. Subjects in Parts 1, 3, and 4 will receive MK-1092 SC or glargine to assess safety, tolerability, PK, and PD from this mode of delivery. Healthy adult subjects in Part 2 will receive MK-1092 as well as an infusion of Humalog to explore the glucose-lowering potential of Humalog infusion after SC administration of MK-1092. Initiation of Part 2 occurred after safety and tolerability of 8.0 nmol/kg dose after SC administration in Part 1 had been assessed. Adult subjects with T1DM in Part 3 and adult subjects with T2DM in Part 4 will receive MK-1092 SC or glargine to assess safety, tolerability, PK, and PD from this mode of delivery in a target patient population. The first panel of Part 3 tested MK-1092 8.0 nmol/kg SC, a dose demonstrated to be safe and tolerated in healthy subjects, that has achieved GIR \sim 1-2 mg/kg/min in Part 1, and that has been tested with Humalog infusion (Part 2) in healthy adult subjects. The first period of Part 4 will use MK-1092 32 nmol/kg, which was demonstrated to be safe and well-

tolerated in Part 1. Each subject in Part 4 will receive single dose administration in up to three different periods. This approach will allow for assessment of GIR at more than one dose level in subjects with T2DM.

4.2.2.1 Rationale for the Use of Comparator/Placebo

In Parts 1, 3, and 4, glargine insulin will be administered to confirm the PD profile of glargine compared to MK-1092 and to serve as a safety comparator in healthy adult subjects (Part 1), in adult subjects with T1DM (Part 3), and in adult subjects with T2DM (Part 4). To facilitate blinding, subjects participating in Parts 1, 3, and 4 will receive injections of MK-1092/glargine and placebo matched to the alternative active treatment. PD will be assessed as the GIR required to maintain the prespecified euglycemic clamp (~5% below fasting glucose levels for healthy adult subjects or at ~100 mg/dL for adult subjects with T1DM and T2DM). Both glargine and MK-1092 will be administered as a single SC dose. Glargine 3.0 nmol/kg (0.5 units/kg) will be used in all panels of Parts 1 and 3 and all periods of Part 4. Glargine has been chosen as a comparator as it is a commonly used basal insulin in management of T1DM and T2DM. The 3.0 nmol/kg dose achieves GIR ~2 mg/kg/min between 6 and 18 hr after SC dosing in healthy adult subjects [3] and shown to have similar effects on GIR in adult subjects with T1DM [4]. Furthermore, the 3.0 nmol/kg dose has clinical relevance as it falls within a range of glargine used by patients with diabetes. Given underlying insulin resistance in subjects with T2DM, it is anticipated that GIR_{max} following glargine 3.0 nmol/kg will be no higher in adult subjects with T2DM than healthy adult subjects and adult subjects with T1DM.

In Part 2, Humalog will be infused for 3 hr, starting ~12 hr after SC administration of MK-1092. The timing of the Humalog infusion has been chosen to correspond to a time at which MK-1092 is anticipated to have a glycemic effect, though the actual starting time of the Humalog infusion may be altered based on data from Part 1. The dose of IV Humalog (0.2 units/kg = 1.2 nmol/kg over 3 hr) is near the range of insulin used in clinical practice to treat diabetic ketoacidosis. The GIR during IV Humalog infusion after SC administration of MK-1092 was anticipated to be > 4 mg/kg/min, which is a GIR above that required for suppression of hepatic glucose production [5], and likely ~9-11 mg/kg/min, which approaches the maximal GIR observed in the literature [6].

In addition to measuring GIR as a PD endpoint, serum free fatty acids (FFA) or non-esterified fatty acids (NEFA) and plasma glycerol will also be assessed in all parts as a comparator for the lipolysis effect of MK-1092. The PK of glargine will also be assessed in Parts 1, 3 and 4.

4.2.2.2 Starting Dose for This Trial

The proposed starting dose of MK-1092 for this trial is 4.0 nmol/kg SC, which will be administered to healthy adult subjects in Part 1. This starting dose was selected in accordance with regulatory guidelines, which recommend a starting dose of 1/10th the NOAEL at the human equivalent dose (HED) in the more sensitive species, correcting for body surface area. For MK-1092, the more sensitive species for calculating the starting dose is the dog, as it is the species in which the lowest HED can be identified. The NOAEL SC

dose of 3.0 mg/kg/d (255.5 nmol/kg) supports the starting dose of 4.0 nmol/kg SC dose in humans, based on the following:

The bioavailability of MK-1092 in dogs is 0.67, which makes the 3.0 mg/kg/d SC dose roughly equivalent to 2.0 mg/kg IV, or 170 nmol/kg (molecular weight of MK-1092 is 11,751 g/mol = 11,751 mg/mmol). Multiplying 170 nmol/kg * 0.54 (correction for body surface area) = 91.8 nmol/kg * 0.1 (safety factor) = 9.18 nmol/kg. This dose is calculated using the unlikely and highly conservative assumption of 100% bioavailability from SC administration in humans and still has a ~2.3x margin to the proposed initial SC dose of 4.0 nmol/kg. Based on translational PK/PD modeling, the starting dose of 4.0 nmol/kg SC has a projected exposure of 9.1 nM*hr assuming F=0.4, which is the lowest bioavailability observed in pre-clinical species. The observed exposure of MK-1092 4.0 nmol/kg was 9.86 nM*hr, which supports the assumption of F ~ 0.4. The assumption of F=0.4 is used in subsequent calculations unless otherwise specified.

The projected effective range for MK-1092 for clinical administration in both healthy adult subjects and adult subjects with T1DM has been estimated based on preclinical studies and extensive modeling to be 12.6 nmol/kg SC. The projected effective range for MK-1092 in adult subjects with T2DM may be twice as high (~ 25 nmol/kg SC) given the presence of insulin resistance in this population. This is the dose at which the GIR in a euglycemic clamp is expected to run at ~1-2 mg/kg/min, which is a generally accepted GIR for suppression of hepatic glucose production and thus a likely target for clinical dosing. A SC dose of 12.6 nmol/kg is projected to lead to an exposure (AUC_{0-24hr} at steady state) of 29 nM*hr, assuming linear PK. A range of exposure around this predicted therapeutic dose was anticipated in Part 1 between Panels B (8.0 nmol/kg SC) and C (16 nmol/kg SC). The observed AUC_{0-24h} was 12.9 nM*h at 8.0 nmol/kg and 26.0 nM*h at 16 nmol/kg.

There were no adverse toxicities noted in pre-clinical studies. Reductions in blood glucose were observed as would be expected from the pharmacology of an insulin; thus, NOAELs for MK-1092 are derived from the top doses in both rat (20 mg/kg/d SC) and dog (3.0 mg/kg/d SC), which led to exposures of 3650 nM*hr and 479 nM*hr at 2 weeks, respectively. The exposure margin is based on the dog levels and is thus ~52x for the 4.0 nmol/kg starting dose and ~16x for the 12.6 nmol/kg SC projected therapeutic dose.

For Part 2, in which healthy adult subjects will be infused with Humalog after SC administration of MK-1092, the dose of MK-1092 that achieves the GIR_{max} of ~1-2 mg/kg/min in Part 1 will be used. Therefore, Part 2 will not start until the starting dose to be used has been explored in Part 1 (without co-administration with Humalog). The dose that achieves GIR ~1-2 mg/kg/min will be used in Part 2 because it is a dose that will suppress hepatic glucose production and nears the target GIR for MK-1092 in healthy adult subjects and in adult subjects with T1DM.

For Part 3, in which adult subjects with T1DM are receiving MK-1092 via SC injection, the first dose was 8.0 nmol/kg, as determined by data from Part 1. Specifically, the starting dose in Part 3 will be no higher than a safe and tolerated dose that achieves GIR ~1-2 mg/kg/min (Part 1) and that has been tested with Humalog infusion (Part 2) in healthy adult subjects. Dosing in Part 3 started after completion of the SC MK-1092 panel at the same or higher

dose in healthy adult subjects in Parts 1 and 2. Dosing in all subsequent panels of Part 3 will commence upon review of the safety data from previous panels within Part 3 and determination of an acceptable safety profile to continue dose escalation. The therapeutic exposure is expected to be similar in healthy adult subjects and adult subjects with T1DM.

For Part 4, in which adult subjects with T2DM are receiving MK-1092 via SC injection, the first dose will be 32 nmol/kg, which is below the highest dose tested in Part 1 as of the time of protocol amendment 03 (64 nmol/kg MK-1092), and which was safe and well-tolerated. Dosing in all subsequent periods of Part 4 will commence upon review of the safety data from previous periods and determination of an acceptable safety profile to continue dose escalation. The therapeutic exposure is expected to be higher in adult subjects with T2DM than in healthy subjects or adult subjects with T1DM given the presence of greater insulin resistance.

Up to 3 doses of MK-1092 in Part 3 and up to 3 doses of MK-1092 in Part 4 will be administered in succession in each part; however, Part 3 and Part 4 may be dosed in parallel. The highest dose of MK-1092 in Part 3 and Part 4 will not exceed 64 nmol/kg SC, which is the highest planned clinical dose. Adult subjects with T1DM and T2DM may also be randomized to glargine in Part 3 and Part 4. The 3.0 nmol/kg dose (0.5 units/kg) of glargine is anticipated to achieve GIR \sim 2 mg/kg/min based on the literature [4] and is clinically relevant as it approximates a commonly used amount of insulin for patients with diabetes.

4.2.2.3 Maximum Dose/Exposure for This Trial

In preclinical toxicity studies, reductions in blood glucose, which were not considered adverse, were observed in both rat and dog. Biliary duct findings, which were also not considered adverse, were observed in the dog only. 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 and at least 3 dose levels were assessed in both.

The upper range for dosing in this study has been selected based on preclinical studies, emerging clinical data, and extensive modeling to provide exposure levels several fold above those projected to be needed in subsequent clinical studies. For example, the therapeutic exposure level for insulin resistant subjects with T2DM is estimated to be 58 nM*h, which is twice that for healthy adult subjects and adult subjects with T1DM. Thus, the maximum dose in this study of 64 nmol/kg is projected to lead to an exposure (AUC_{0-∞}) of 146 nM*hr, or \sim 2.5x that required for therapeutic exposure in T2DM. In the highly unlikely setting of F=1, exposure at 64 nmol/kg SC could be 366 nM*hr, a value which is provided only as a highly conservative benchmark.

As noted above, the lower NOAEL was observed in dog, in which a dose of 3.0 mg/kg/d SC led to an AUC_{0-24hr} level of 479 nM*hr on the last day of dosing. According to regulatory guidance, the maximum clinical dose should not lead to exposure levels that exceed this level. The maximum SC dose of 64 nmol/kg has a predicted exposure margin for AUC_{0-∞} of \sim 3.3x assuming F=0.4 or \sim 1.3x assuming the highly unlikely F=1. Therefore, safety margins for this maximum planned clinical dose are adequate. Further, this dose may not be

administered if PD targets have been reached at earlier doses, if there are unexpected safety findings or if a revised projected exposure based on PK obtained during this trial would not lead to a satisfactory margin. With respect to the reductions in blood glucose seen in the preclinical toxicity studies, note that subjects in this trial will be receiving a glucose infusion via the euglycemic clamp. Subjects will be intensively monitored, with frequent assessment of blood glucose, even after discontinuation of the clamp.

4.2.2.4 Rationale for Dose Interval and Trial Design

MK-1092 is an insulin analog and thus will likely affect blood glucose, especially at higher doses. As such, this study will use a continuous glucose infusion during the euglycemic clamp so that glucose levels remain in the euglycemic range and hypoglycemia is prevented. To this end, blood glucose will be monitored frequently (~every 5 minutes), allowing rapid changes to the rate of glucose infusion. In addition to maintaining safety by avoiding hypoglycemia, the glucose infusion rate (GIR) will be the primary PD readout, as noted elsewhere.

In Part 1, six healthy adult subjects will be administered a SC dose of MK-1092 and two healthy adult subjects will be administered a SC dose of glargine 3.0 nmol/kg (0.5 units/kg) in each panel. Decisions to increase, decrease, or repeat SC dosing levels in Part 1 will be based on safety and tolerability data from prior panels.

In Part 1, healthy adult subjects will remain on the euglycemic clamp until the GIR has stabilized near 0 mg/kg/min and glucose infusion can be discontinued safely, at the discretion of the investigator. In a study of healthy adult subjects, glargine 3.0 nmol/kg (0.5 units/kg) SC demonstrated glucose-lowering activity during 24 h after administration with a GIR_{max} of 2.1-2.8 mg/kg/min [3]. Evidence from preclinical studies indicates that MK-1092 will have glucose lowering effect over at least 18 hr after SC administration. Subjects will be receiving a simultaneous infusion of glucose, with frequent assessment of blood glucose and necessary adjustments of the GIR to maintain glucose levels at the pre-specified level. While GIR may not return to a level close to 0 mg/kg/min at the same time in subjects receiving glargine and MK-1092 SC, all subjects will continue to be monitored similarly, to ensure both safety and blinding.

In Part 2, four healthy adult subjects will be administered a SC dose of MK-1092. The glycemic effect of IV Humalog following SC administration of MK-1092 will be examined in the single panel of this part. The dosing level of MK-1092 8.0 nmol/kg was determined from data in Part 1, and was communicated with the site by a Protocol Clarification Letter prior to the dosing in Part 2. Subjects will receive MK-1092 at a dose expected to lead to a GIR ~1-2 mg/kg/min. Subjects will also receive a 3 hr infusion of Humalog 1.2 nmol/kg IV (0.2 units/kg) at approximately 12 hr after SC administration of MK-1092, a time at which MK-1092 is anticipated to have a glycemic effect. The actual start time of Humalog infusion was confirmed as 12 h post-dose in a Protocol Clarification Letter prior to the dosing in Part 2. As in Part 1, the GIR will be adjusted as necessary to maintain the pre-specified blood glucose level and subjects will remain on the euglycemic clamp until the GIR has stabilized near 0 mg/kg/min and glucose infusion can be discontinued safely, at the discretion of the investigator.

In Part 3, six adult subjects with T1DM will be administered a SC dose of MK-1092 and two adult subjects with T1DM will be administered a SC dose of glargine 3.0 nmol/kg (0.5 units/kg) in each panel. The dose in Panel G will be determined following review of data from Part 1 and will be no higher than a safe and tolerated dose that achieves GIR ~1-2 mg/kg/min (Part 1) and has been tested with Humalog infusion (Part 2) in healthy adult subjects. As of the timing of amendment 03, the dose of 8.0 nmol/kg had fulfilled these requirements and was tested in Part 3 Panel G. Decisions to increase, decrease, or repeat SC dosing levels in Part 3 will be based primarily on safety and tolerability data from prior panels in Part 3, and doses may be increased up to the planned maximum clinical dose of 64 nmol/kg SC. The dose of Part 3 Panel G was communicated to the site by Protocol Clarification Letter prior to dosing.

In Part 3, the clamp will be completed when blood glucose is > 150 mg/dL for 30 minutes in the absence of exogenous glucose infusion or sooner at the discretion of the investigator; exogenous insulin will be given at this time. The duration of glycemic effect for glargine and MK-1092 in adult subjects with T1DM is anticipated to be the same as in healthy adult subjects. Subjects will be receiving a simultaneous infusion of glucose, with frequent assessment of blood glucose and necessary adjustments of the GIR to maintain glucose levels at the pre-specified level. While the clamp may not be completed at the same time in subjects receiving glargine and MK-1092 SC, all subjects will continue to be monitored similarly, to ensure both safety and blinding. After completion of the euglycemic clamp, adult subjects with T1DM will eat and resume their pre-study insulin regimen; however, they will continue to wear and use the insulin pump as needed until glycemic control has been re-established using the pre-study insulin therapy.

In Part 4, six adult subjects with T2DM will be administered a SC dose of MK-1092 and three adult subjects with T2DM will be administered a SC dose of glargine 3.0 nmol/kg (0.5 units/kg). Subjects who receive MK-1092 in Period 1 will receive MK-1092 in subsequent periods, and subjects who receive glargine in Period 1 will receive glargine in subsequent periods. The dose in Period 1 will be 32 nmol/kg based on this dose being a safe and tolerated dose in Part 1. Decisions to increase, decrease, or repeat SC dosing levels in Part 4 will be based primarily on safety and tolerability data from prior periods in Part 4, and doses may be increased up to the planned maximum clinical dose of 64 nmol/kg SC.

In Part 4, the clamp will be completed when blood glucose is > 150 mg/dL for 30 minutes in the absence of exogenous glucose infusion or sooner at the discretion of the investigator; pre-study anti-diabetic therapy, including insulin if appropriate, will be given following the end of the clamp at the discretion of the investigator. The duration of glycemic effect for glargine and MK-1092 in adult subjects with T2DM is anticipated to be the same as in healthy adult subjects. Subjects will be receiving a simultaneous infusion of glucose, with frequent assessment of blood glucose and necessary adjustments of the GIR to maintain glucose levels at the pre-specified level. While the clamp may not be completed at the same time in subjects receiving glargine and MK-1092 SC, all subjects will continue to be monitored similarly, to ensure both safety and blinding. After completion of the euglycemic clamp, adult subjects with T2DM will eat; the pre-study anti-diabetic regimen will be started following the end of the clamp at the investigator's discretion. Those subjects requiring insulin pump during the

study will continue to wear and use the insulin pump as needed until glycemic control has been re-established using the pre-study insulin therapy and any other background therapy.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

As this is an early clinical investigation of MK-1092, 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-1092. Preclinical toxicology studies in rats and dogs did not demonstrate any adverse findings of concern and showed expected mechanism-based reductions in blood glucose. 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 adequate 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 Appendix 12.4 for details). Standard chemistry, hematology and urinalysis panels will be assessed along with careful and frequent glucose monitoring.

MK-1092 administration could lead to anti-drug antibody (ADA) formation, which because of the nature of MK-1092 could also result in neutralizing antibodies that cross-react with insulin, thus forming anti-insulin antibodies (AIAs) that could result in insulin resistance. ADA and AIA will be assessed pre-dose and on Day 14 and Day 28 following cessation of treatment (see Section 7.1.5.3 for post-trial follow-up). The changes in PD marker (blood glucose levels) will serve as a measure of potential neutralizing activity of ADA. Samples will be collected and banked for future analysis if clinical observations warrant such a need. To reduce the risk of ADA and AIA formation, only one MK-1092 administration per subject was planned for Parts 1-3.

At the time of protocol amendment 04, no formation of ADA had been observed in healthy adult subjects in Part 1 Panels A-D, Part 2, or Part 3 Panels G and H at 14 or 28 days after one administration of MK-1092. In Part 1 Panel E, no ADA or AIA have been detected at 14 or 28 days in 7 of 8 subjects; the 8th subject was lost to follow-up after 14 days and no ADA and AIA had been detected at up to 14 days. Based on these data, the risk of ADA development is anticipated to be minimal for subjects with T2DM (in Part 4) to receive more than one administration of MK-1092.

4.2.3.2 Pharmacokinetic Endpoints

The PK profile of MK-1092 will be assessed in all parts of the trial. Subjects in Parts 1, 3, and 4 will have a single sample collected for glargine or MK-1092 PK, so treatment will remain blinded. Sufficiently sensitive assays for MK-1092 have been developed that will

allow determination of concentrations even at the lower dose levels in this protocol. No urine will be collected for PK.

In Parts 1, 3, and 4, PK assessment will be critical in understanding PD. Specifically, the PD endpoint (GIR_{max} , see below) will be coupled with plasma MK-1092 concentration to determine the concentration–GIR response of MK-1092. Similarly, the PD endpoint of GIR_{max} will also be coupled with glargine concentration for those subjects receiving glargine in Parts 1, 3, and 4. In addition, C_{max} and T_{max} , plasma exposure ($AUC_{0-\infty}$) will also be measured, as will apparent terminal half-life ($t_{1/2}$) reflective of the absorption half-life after SC administration.

In Part 2, PK of MK-1092 will be collected throughout the infusion, similar to as in Part 1 but at slightly different time points to correspond with the timing of Humalog infusion. After Humalog administration, samples will continue to be collected for MK-1092 PK as well as additional samples will be collected for Humalog PK.

4.2.3.3 Pharmacodynamic Endpoints

The primary objective in this study, in addition to the evaluation of safety, is to gain an understanding of the short term glycemic effects of MK-1092 as determined by GIR, as this will predict the ability of MK-1092 to function as a basal insulin with wide TI. Evaluation of lipolysis markers will also be performed.

Euglycemic clamp is used in this study to determine the dose range in which MK-1092 is able to suppress hepatic glucose production without largely stimulating muscle glucose uptake. The effect of MK-1092 will be compared with that of glargine when administered at doses that also suppress hepatic glucose output. At euglycemia, high doses of full agonist insulins such as Humalog require a maximum GIR of approximately 10-11 mg/kg/min to prevent hypoglycemia, reflecting a combination of suppressed hepatic glucose production (HGP) and insulin-mediated glucose disposal, primarily into muscle. 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][7]. 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. In a recent trial of the hepatoselective insulin peglispro, the highest GIR was around 4 mg/kg/min across a wide range of doses tested [8] which included a mild effect on presumed muscle uptake. The range of acceptable GIR_{max} (1.5-4.5 mg/kg/min) in adult subjects with T1DM was selected to bracket the target GIR of ~2 mg/kg/min. Preclinical data show that IRPAs have greater glycemic effect in diabetic models. GIR will be adjusted to maintain blood glucose levels at ~5% lower than the baseline fasted glucose levels for healthy adult subjects or ~100 mg/dL for adult subjects with T1DM and T2DM. After and during the dosing of MK-1092 or glargine, glucose levels will be monitored at the bedside and the GIR will be adjusted accordingly. The values of interest from the GIR are the individual GIR_{max} during the euglycemic clamp (Parts 1, 3, and 4), or individual GIR_{max} during infusion of Humalog (Part 2). In Part 1, GIR may differ in the subjects who receive MK-1092 and glargine, particularly in early panels which will use lower doses of MK-1092. In Part 3, GIR is anticipated to be similar in the adult subjects with T1DM randomized to MK-1092 and glargine SC at the initial dose tested in Panel G; however, GIR may increase among adult subjects with T1DM

randomized to MK-1092 vs. glargine in subsequent panels as the dose of MK-1092 is escalated but glargine dose is unchanged. In Part 4, GIR may be higher in adult subjects with T2DM randomized to MK-1092 vs. glargine SC given planned doses of 32 nmol/kg in Period 1 and ≤ 64 nmol/kg in Periods 2 and 3.

Insulin regulates lipolysis and ketosis in normal physiology, and MK-1092 is expected to have this activity as well. To evaluate the effect on lipolysis, serum non-esterified fatty acids (NEFA, also known as FFA or free fatty acids) and plasma glycerol will be assessed in all parts. To assess ketosis, β -hydroxybutyrate will be assessed. NEFA, glycerol, and β -hydroxybutyrate will be correlated with MK-1092 PK and glucose PD to more fully understand the complete PD profile for MK-1092.

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.

Anti-Insulin and Anti-MK-1092 Antibodies

Both anti-insulin antibodies (AIA) and anti-drug antibodies (ADA) will be collected pre- and post-dosing in all 4 parts.

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

Subjects in clinical trials generally cannot expect to receive direct 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

Healthy male and female subjects (of non-child bearing potential) between the ages of 18 and 50 years (inclusive); male and female subjects (of non-child bearing potential) with T1DM between the ages of 18 and 60 years (inclusive); and male and female subjects (of non-child bearing potential) with T2DM between the ages of 18 and 60 years (inclusive) 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 Parts 1 and 2 (Healthy adult subjects)

1. Subjects provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be a healthy male, or healthy female subject of non-child bearing potential between 18 and 50 years of age (inclusive) at the prestudy (screening) visit.

A female of non-child bearing 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 at pretrial (screening), and/or
- b. A female whose status is post hysterectomy, bilateral 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; bilateral oophorectomy may be confirmed by hormone levels, particularly FSH in the postmenopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents

3. Have a Body Mass Index (BMI) $\geq 18.5 \text{ kg/m}^2$ and $\leq 28.0 \text{ kg/m}^2$ at screening. BMI=weight (kg)/height (m)².
4. Be judged to be in good health based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Appendix 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria.
5. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at the screening visit and from the laboratory safety tests obtained pre-dosing, prior to administration of the initial dose of trial drug. Appendix 12.5 provides an algorithm for the assessment of out-of-range laboratory values.
6. Fasting blood glucose values at screening must be $< 100 \text{ mg/dL}$. This may be repeated on a second screening day at the discretion of the investigator.
7. Be a nonsmoker and/or has not used nicotine or nicotine-containing products (e.g., nicotine patch) for at least approximately 3 months.
8. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).
9. Have adequate venous access to support execution of trial procedures.

For Part 3 (Adult subjects with T1DM):

1. Subjects provide written informed consent for the trial. The subject may also provide consent 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 (inclusive) 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, bilateral oophorectomy or tubal ligation.

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; bilateral 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. Have a diagnosis of T1DM as defined by standard diagnostic criteria for ≥ 12 months at time of the pretrial (screening) visit.

4. Have a Body Mass Index (BMI) $\geq 18.5 \text{ kg/m}^2$ and $\leq 32.0 \text{ kg/m}^2$ at screening. BMI = weight (kg)/height (m)².
5. Be judged to be in good health based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Appendix 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria. Subjects in Part 3 will all have T1DM. Subjects with the following conditions may also 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. 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. 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. For subjects with known non-proliferative diabetic retinopathy, a dilated ophthalmic exam must have been performed within 18 months of screening. If an exam was not performed within 18 months of screening, a dilated ophthalmic exam must be performed during the screening period either by their own ophthalmologist or an ophthalmologist associated with the clinical research unit. Subjects with other diagnosed complications of diabetes, such as peripheral neuropathy and/or moderately increased albuminuria (i.e., microalbuminuria ≥ 30 and ≤ 300 mg urine albumin/g urine creatinine), may also be included. Urine microalbumin must be assessed at screening unless it has been confirmed to be ≤ 300 mg urine albumin/g urine creatinine within 12 months of screening.
 - d. 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.
 - 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.
6. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at the screening visit and from the laboratory safety tests obtained pre-dosing, prior to administration of the initial dose of trial drug. Appendix 12.5 provides an algorithm for the assessment of out-of-range laboratory values.
7. Have a serum C-peptide concentration $\leq 0.7 \text{ ng/mL}$ (0.23 nM) with a concurrent plasma glucose $>90 \text{ mg/dL}$ (5 mM) at screening or any time within 24 weeks prior to screening. If necessary, the subject may consume carbohydrates to raise plasma

- glucose over 90 mg/dL (5 mM) as measured by point of care analyzer (YSI or GlucoScout) prior to drawing blood for C-peptide.
8. 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 $\pm 20\%$ difference in total daily insulin doses. Insulin pump users will be allowed.
 9. Have a total daily insulin requirement (basal plus prandial) of ≤ 1.2 units/kg at screening.
 10. Have a HbA1c $\leq 10\%$ at the screening visit.
 11. 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). Smoking and/or the use of nicotine/nicotine-containing products) is not permitted during the trial.
 12. Be willing to comply with the trial restrictions (see Section 5.7 for a complete summary of trial restrictions).
 13. Have adequate venous access to support execution of trial procedures.

For Part 4 (Adult subjects with T2DM):

1. Subjects provide written informed consent for the trial. The subject may also provide consent 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, bilateral 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; bilateral oophorectomy may be confirmed by hormone levels, particularly FSH in the postmenopausal range, but tubal ligation subjects without records should be excluded. Information must be captured appropriately within the site's source documents
3. Have a diagnosis of T2DM as defined by standard diagnostic criteria for ≥ 12 months at time of pretrial (screening) visit.
 4. Have a BMI ≥ 18.5 kg/m² and ≤ 35.0 kg/m² at screening. BMI = mass (kg)/height (m)².
 5. Have a HbA1c $\geq 6.5\%$ and $\leq 10.0\%$.

6. Be judged to be in good health based on medical history, physical examination, vital sign measurements and ECG performed prior to randomization. Appendix 12.4 provides a table of 12-Lead Electrocardiogram Abnormality Criteria. Subjects in Part 4 will all have T2DM. Subjects with the following conditions may also 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. 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. For subjects with known non-proliferative diabetic retinopathy, a dilated ophthalmic exam must have been performed within 18 months of screening. If an exam was not performed within 18 months of screening, a dilated ophthalmic exam must be performed during the screening period either by their own ophthalmologist or an ophthalmologist associated with the clinical research unit. Subjects with other diagnosed complications of diabetes, such as peripheral neuropathy and/or moderately increased albuminuria (i.e., microalbuminuria ≥ 30 and ≤ 300 mg urine albumin/g urine creatinine), may also be included. Urine microalbumin must be assessed at screening unless it has been confirmed to be ≤ 300 mg urine albumin/g urine creatinine within 12 months of screening.
 - 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.
7. Be judged to be in good health based on laboratory safety tests (Section 7.1.3.1) obtained at the screening visit and from the laboratory safety tests obtained pre-dosing, prior to administration of the initial dose of trial drug. Appendix 12.5 provides an algorithm for the assessment of out-of-range laboratory values.
8. T2DM subjects are not required to have been on insulin. If using insulin as background therapy, 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 $\pm 20\%$ difference in total daily insulin doses. Insulin pump users will be allowed.

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).
11. Have adequate venous access to support execution of trial procedures.

5.1.3 Subject Exclusion Criteria

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

For Parts 1 and 2 (Healthy adult subjects)

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 (i.e. requiring medication and/or therapy beyond counseling) 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, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary or major neurological (including stroke and chronic seizures) abnormalities or diseases. Subjects with a history of minor and/or remote events (e.g. 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.
4. Has a systolic blood pressure (SBP) \geq 140 mm Hg and/or a diastolic blood pressure (DBP) \geq 90 mm Hg at screening.
 - a. Resting semi-recumbent blood pressure will be assessed at screening. The median of 3 measurements taken within a 10-minute period (all 3 sets completed within 10 minutes) must meet the criteria noted above. If not met on the first screening day, this may be repeated on a second screening day at the discretion of the study investigator.
5. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV at screening.
6. 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 \geq 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 6); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

7. Subject has an estimated creatinine clearance of < 90 mL/min based on the Cockcroft-Gault equation; the Cockcroft-Gault equation is (for females multiply result by 0.85) at screening:

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

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

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

8. 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.
9. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
10. 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.
11. Has been randomized to, and received, MK-5160 in prior clinical studies.
12. Has a QTcF 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).
13. Has uncorrected hypokalemia (below lower limit of normal of local lab reference) at screening. Potassium levels may be corrected, and if normal on repeat, the subject may be included.
14. Has uncorrected hypomagnesemia (below lower limit of normal of local lab reference) at screening. Magnesium levels may be corrected, and if normal on repeat, the subject may be included.
15. Is taking concomitant medications that prolong the QT/QTc interval.
16. 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, until the post-trial visit. See the Inclusion Criteria and Section 5.5 for discussion of medications and multivitamins that may be permitted. As noted in Section 5.5, ibuprofen use is permissible.
17. Has had a vaccination within 12 weeks of the pretrial visit. Subjects who have received influenza or Hepatitis A vaccine within 12 weeks of the pretrial visit may be included at the discretion of the investigator and Sponsor.
18. 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.

19. 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.
20. Is currently a regular or recreational user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 6 months. Subjects must have a negative urine drug screen (UDS) prior to randomization.
21. Has used systemic (intravenous, oral, inhaled) glucocorticoids within 3 months of screening or is anticipated to require treatment with systemic glucocorticoids during study participation.
22. Elicits 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.
23. 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 3 (Adult subjects with 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 (i.e. requiring medication and/or therapy beyond counseling) 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 minor and/or remote events (e.g. 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 systolic blood pressure (SBP) \geq 140 mm Hg and/or a diastolic blood pressure (DBP) \geq 90 mm Hg at screening.
 - a. Resting semi-recumbent blood pressure will be assessed at screening. The median of 3 measurements taken within a 10-minute period (all 3 sets completed within 10 minutes) must meet the criteria noted above. If not met on the first screening day, this may be repeated on a second screening day at the discretion of the study investigator.
5. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV at screening.
6. 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 6); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.

7. 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) at screening:

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

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

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

8. 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.
9. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
10. 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.
11. Has been randomized to, and received, MK-5160 in prior clinical studies.
12. Has a QTcF 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).
13. Has uncorrected hypokalemia (below lower limit of normal of local lab reference) at screening. Potassium levels may be corrected, and if normal on repeat, the subject may be included.
14. Has uncorrected hypomagnesemia (below lower limit of normal of local lab reference) at screening. Magnesium levels may be corrected, and if normal on repeat, the subject may be included.
15. Is taking concomitant medications that prolong the QT/QTc interval.
16. Is unable to refrain from or anticipates the use of any medication (aside from insulin and approved 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, until the post-trial visit. See the Inclusion Criteria and

- Section 5.5 for discussion of medications, such as antihypertensives, HMG-CoA reductase inhibitors (statins), and aspirin, and multivitamin that may be permitted.
17. Has had a vaccination within 12 weeks of the pretrial visit. Subjects who have received influenza or Hepatitis A vaccine within 12 weeks of the pretrial visit may be included at the discretion of the investigator and Sponsor.
 18. 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.
 19. 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.
 20. Is currently a regular or recreational user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 6 months. Subjects must have a negative urine drug screen (UDS) prior to randomization.
 21. Has a history of diabetic ketoacidosis in the last 6 months prior to screening.
 22. 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.
 23. Has used systemic (intravenous, oral, inhaled) glucocorticoids within 3 months of screening or is anticipated to require treatment with systemic glucocorticoids during study participation.
 24. Has other major medical problems requiring medication. 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 may be included in the trial at the discretion of the Investigator and Sponsor.
 25. Has a known history of celiac disease or significant food allergy, at the discretion of the investigator and Sponsor.
 26. Has a history of hypersensitivity to pharmacologic insulins or to any of the inactive ingredients in recombinant human insulin, or to any E.coli-derived drug product.
 27. Elicits 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.
 28. 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 4 (adult subjects with 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 (i.e. requiring medication and/or therapy beyond counseling) 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 minor and/or remote events (e.g. 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 systolic blood pressure (SBP) \geq 150 mm Hg and/or a diastolic blood pressure (DBP) \geq 95 mm Hg at screening.
 - a. Resting semi-recumbent blood pressure will be assessed at screening. The median of 3 measurements taken within a 10-minute period (all 3 sets completed within 10 minutes) must meet the criteria noted above. If not met on the first screening day, this may be repeated on a second screening day at the discretion of the study investigator.
5. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV at Screening.
6. 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 \geq 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 6); or, (3) Subjects, who, in the opinion of the trial investigator, are highly unlikely to sustain a recurrence for the duration of the trial.
7. 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):

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

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

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

8. Has a history of significant multiple and/or severe allergies (e.g. food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerance (i.e. systemic allergic reaction) to prescription or non-prescription drugs or food.
9. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.
10. 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.
11. Has been randomized to, and received, MK-5160 in prior clinical studies.
12. 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).
13. Has uncorrected hypokalemia (below lower limit of normal of local lab reference) at screening. Potassium levels may be corrected, and if normal on repeat, the subject may be included.
14. Has uncorrected hypomagnesemia (below lower limit of normal of local lab reference) at screening. Magnesium levels may be corrected, and if normal on repeat, the subject may be included.
15. Is taking concomitant medications that prolong the QT/QTc interval
16. Is unable to refrain from or anticipates the use of any medication (aside from approved 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, until the post-trial visit. See the Inclusion Criteria and Section 5.5 for discussion of medications, such as insulin, non-insulin anti-diabetic medications, antihypertensives, HMG-CoA reductase inhibitors (statins), and aspirin, and multivitamin that may be permitted.
17. Has had a vaccination within 12 weeks of the pretrial visit. Subjects who have received influenza or Hepatitis A vaccine within 12 weeks of the pretrial visit may be included at the discretion of the investigator and Sponsor.
18. 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.
19. 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.
20. Is currently a regular or recreational user of cannabis, 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.

21. Has a history of diabetic ketoacidosis in the last 6 months prior to screening.
22. 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.
23. 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
24. Has a known history of celiac disease or significant food allergy, at the discretion of the Investigator and Sponsor.
25. Has used systemic (intravenous, oral, inhaled) glucocorticoids within 3 months of screening or is anticipated to require treatment with systemic glucocorticoids during study participation.
26. Has been treated with a thiazolidinedione or injectable non-insulin anti-diabetic therapy within the past three months prior to dosing.
27. 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.
28. 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 treatments to be used in this trial are outlined below in [Table 2](#).

Table 2 Trial Treatments

| Drug | Dose/ Potency | Dose Frequency | Route of Administration | Regimen/ Treatment Period | Use |
|--------------------------------|--|---|------------------------------------|---|--------------------------------|
| MK-1092 | Potency: 20 mg/mL | One time dose | Subcutaneous | Parts 1-4, all panels/periods | Experimental |
| Glargine | 100 units/mL | One time dose | Subcutaneous | Parts 1, 3, and 4, all panels/periods | Active Comparator |
| Dextrose | 20% solution; adjusted to maintain target glycemic levels during euglycemic clamp | Continuous infusion for the duration of the clamp (as needed to maintain blood sugar at pre-clamp target of 5% below fasting levels for healthy adult subjects or ~100 mg/dL for T1DM/T2DM) | Intravenous | Parts 1-4, all panels/periods | Glucose Clamp Assessment |
| Insulin Humalog (lispro) | One time dose of 0.2 U/kg | One time infusion over 3 hours | Intravenous | Part 2 | Experimental Assessment |
| Saline (Matched Placebo) | Not applicable | One time dose | Subcutaneous | Parts 1, 3 and 4, all panels/periods | 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 2](#) (except MK-1092) 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-1092 and 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.

Humalog will be prepared as per the instructions outlined in the Study Operations Manual. Infusion of Humalog will occur (in Part 2) approximately twelve hours after SC dosing of MK-1092, a time at which MK-1092 is anticipated to have a glycemic effect and GIR may be near maximal following MK-1092 administration.

5.2.3 Trial Blinding

Part 2 is open-label; therefore, the Sponsor, investigator and subject will know the treatment administered.

For Parts 1, 3 and 4, a double-blinding technique will be used. MK-1092 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 participating in Parts 1, 3 and 4 will receive injections of MK-1092/glargine and placebo matched to the alternative active treatment (i.e. subjects will receive either MK-1092 and glargine-matched placebo, or glargine and MK-1092-matched placebo).

See Section 7.1.4.2, Subject 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 participating in Parts 1, 3 and 4 of this trial will be assigned randomly according to a computer-generated allocation schedule. Sample allocation schedules for Parts 1, 3 and 4 are provided in [Table 3](#), [Table 5](#) and [Table 6](#), respectively.

Subjects participating in Part 2 of this trial will be allocated by non-random assignment. A sample allocation schedule for Part 2 is provided in [Table 4](#).

Table 3 Sample Allocation Schedule (Part 1)

| Subjects (NHV) | Panel A | Panel B | Panel C | Panel D | Panel E |
|-----------------------|------------------------------|------------------------------|----------------------------|----------------------------|----------------------------|
| N=6 | MK-1092 4.0 nmol/kg SC | | | | |
| N=2 | Glargine 3.0 nmol/kg SC | | | | |
| N=6 | | MK-1092 8.0 nmol/kg SC | | | |
| N=2 | | Glargine 3.0 nmol/kg SC | | | |
| N=6 | | | MK-1092 16 nmol/kg SC | | |
| N=2 | | | Glargine 3.0 nmol/kg SC | | |
| N=6 | | | | MK-1092 32 nmol/kg SC | |
| N=2 | | | | Glargine 3.0 nmol/kg SC | |
| N=6 | | | | | MK-1092 64 nmol/kg SC |
| N=2 | | | | | Glargine 3.0 nmol/kg SC |

SC – Subcutaneous; NHV – Normal Healthy Volunteer
 Subjects will only participate in one panel.
 The suggested dose may be adjusted downward based on evaluation of safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous panels.
 To maintain blinding, subjects will receive two injections at each administration – one active (MK-1092 or glargine) and one placebo due to potential differing volumes of the active treatments.

Table 4 Sample Allocation Schedule (Part 2)

| Subjects (NHV) | Panel F |
|-----------------------|--|
| N=4 | MK-1092 SC (8.0 nmol/kg dose based on Part 1) + Humalog 1.2 nmol/kg IV |

SC – Subcutaneous; IV – Intravenous; NHV – Normal Healthy Volunteer
 The dose of MK-1092 will be the dose that leads to a GIR of approximately 1-2 mg/kg/min, and will be based on the results of Part 1.

Table 5 Sample Allocation Schedule (Part 3)

| Subjects (T1DM) | Panel G | Panel H | Panel I [†] | Panel J |
|-----------------|--|-------------------------|---------------------------------|---------------------------------|
| N=6 | MK-1092 SC (8.0 nmol/kg based on Part 1) | | | |
| N=2 | Glargine 3.0 nmol/kg SC | | | |
| N=6 | | MK-1092 SC (32 nmol/kg) | | |
| N=2 | | Glargine 3.0 nmol/kg SC | | |
| N=6 | | | MK-1092 SC (≤ 64 nmol/kg) | |
| N=2 | | | Glargine 3.0 nmol/kg SC | |
| N=6 | | | | MK-1092 SC (≤ 64 nmol/kg) |
| N=2 | | | | Glargine 3.0 nmol/kg SC |

SC – Subcutaneous; T1DM – Type 1 Diabetes Mellitus
 Subjects will only participate in one panel.
 The starting dose of MK-1092 in Panel G was 8.0 nmol/kg based on the results of Part 1. Doses for Panels H-J will be determined following review of the safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous panels and will not exceed a maximum dose of 64 nmol/kg.
 To maintain blinding, subjects will receive two injections at each administration – one active (MK-1092 or glargine) and one placebo due to potential differing volumes of the active treatments.
[†]Panel I will be omitted per PCL #10.

Table 6 Sample Allocation Schedule (Part 4)

| Subjects (T2DM) | Period 1 | Period 2 | Period 3 |
|-----------------|-------------------------|-------------------------|---------------------------------|
| N=6 | MK-1092 SC (32 nmol/kg) | MK-1092 SC (16 nmol/kg) | MK-1092 SC (≤ 64 nmol/kg) |
| N=3 | Glargine 3.0 nmol/kg SC | Glargine 3.0 nmol/kg SC | Glargine 3.0 nmol/kg SC |

SC – Subcutaneous; T2DM – Type 2 Diabetes Mellitus
 Subjects will participate in all periods. Subjects who receive MK-1092 in Period 1 will receive MK-1092 in subsequent periods, and subjects who receive glargine in Period 1 will receive glargine in subsequent periods.
 The starting dose of MK-1092 in Period 1 will be 32 nmol/kg based on the results of Part 1. Doses for Periods 2 and 3 will be determined following review of the safety, tolerability, pharmacokinetic and/or pharmacodynamic data observed in previous periods and will not exceed a maximum dose of 64 nmol/kg.
 To maintain blinding, subjects will receive two injections at each administration – one active (MK-1092 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)

If a subject does not discontinue all prior medications within 14 days or 5 half-lives of starting the trial, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the trial.

Concurrent use of any prescription or non-prescription medication, or concurrent vaccination, during the course of the trial (i.e., after randomization or treatment allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The subject will be allowed to continue in the trial if both the Sponsor and the investigator agree.

For healthy adult subjects (Parts 1 and 2) ibuprofen may be used for minor ailments without prior consultation with the Sponsor, and is permissible to have been taken prior to the trial.

For adult subjects with T1DM (Part 3) and T2DM (Part 4), ibuprofen may also be used for minor ailments without prior consultation with the Sponsor, and is permissible to have been taken prior to the trial. Insulin use is expected by all adult subjects with T1DM and for some subjects with T2DM prior to and during the study. Adult subjects with T1DM and T2DM may continue stable doses of statin drugs and certain antihypertensive medications. In addition, adult subjects with T2DM may take oral anti-diabetic medications, excluding thiazolidinediones, up to admission to the CRU for each period.

A standard daily multivitamin is permitted to be taken up to the time of admission to the CRU (without washout) and may be taken after discharge from the CRU. Subjects taking other dietary supplements or vitamins must first be discussed between the investigator and Sponsor Clinical Director. No dietary supplements are permitted while domiciled in the CRU.

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

1. Acetaminophen/paracetamol use is not allowed by any subjects during the study (Parts 1-4). Acetaminophen/paracetamol is permitted to be taken up to the time of admission to the CRU (without washout) and may be taken after discharge from the CRU.
2. Subjects with a history of hypercholesterolemia requiring medication are excluded from Parts 1-2 of the study. Therefore, lipid-lowering medications, including HMG-CoA reductase inhibitors, are not allowed by any subjects in the study (Parts 1-2). Subjects taking stable doses of HMG-CoA reductase inhibitors are allowed in Part 3 and Part 4.
3. Adult subjects with T1DM or T2DM 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 in Part 3 or Part 4, respectively.
4. Beta-blockers and loop diuretics are not allowed by any subjects in the study (Parts 1-4). Subjects on these medications will be excluded.

5. Systemic glucocorticoids are not allowed by any subjects in the study (Parts 1-4). Subjects on inhaled or topical glucocorticoids may be allowed, at the discretion of the investigator and Sponsor.

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 Restrictions

Fasting requirements for trial procedures, such as but not limited to, laboratory safety evaluations, are specified in Section 7.0.

Subjects will fast from all food and drinks, except water, for at least 8 hours prior to the collection of blood for laboratory safety tests at the pre-trial (screening) and post-trial visits. All subjects will fast overnight for at least 8 hours prior to the start of the clamp and study drug administration procedures on Day 1.

Subjects will remain fasted from all food and drinks except water during the euglycemic clamp and until approximately 1 hour after the end of the clamp procedure. When subjects are not fasting, standard meals will be provided in accordance with the site's standard schedule.

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 and from 24 hours prior to and after trial drug administration in each treatment period. At all other times, 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 and from 12 hours prior to and

after trial drug administration in each treatment period. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (> 6 units: 1 unit=120 mg of caffeine).

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, throughout the trial and until the post-trial visit.

Only light activity (walking) will be permitted within 24 hours of dosing in each treatment period through the time of discharge from the clinical research unit.

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. Abstinence is an alternative lifestyle and subjects practicing abstinence may be included in the trial.

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 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 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 of ≥ 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 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 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.

For Part 4 only, the replacement subject may begin dosing at the subsequent dose level for that part, upon agreement between the investigator and Sponsor.

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. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision and this end of study date supersedes the definitions outlined above. 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.

A primary objective of this early Phase I trial is to identify the maximum safe and well-tolerated dose and/or dosing regimen that achieve pharmacokinetic, pharmacodynamic and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that trial subjects may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels in this trial. This would not be defined as early termination of the trial, but rather an earlier than anticipated achievement of the trial objective(s). If a finding (e.g., pharmacokinetic, pharmacodynamic, efficacy, biologic targets, etc.) from another preclinical or clinical trial using the trial treatment(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this trial, results in the trial(s) or program being stopped for non-safety reasons, this also does not meet the definition of early trial termination.

Early trial termination is defined as a permanent discontinuation of the trial due to unanticipated concerns of safety to the trial subjects arising from clinical or preclinical trials with the trial treatment(s), comparator(s), drug(s) of the same class or methodology(ies) used in this trial.

| All Panels ^a | | | | | | | | | | | | | | | | | | | | | | | |
|---|------------------|------|----------|-------|-------|-----|-----|-----|-----|------|------|------|------|------|-------------------------|------|------|------|-------|-------|----|---|---|
| | Scr ^b | D -1 | D1 | | | | | | | | | | | D 2 | | | D3 | D4 | D5 | D6 | D8 | Post-trial (Day 14 +/- 2 days) ^t | Post-trial (Day 28 +/- 3 days) ^t |
| | | | Pre-dose | 0 | 1 h | 2 h | 4 h | 6 h | 9 h | 12 h | 18 h | 24 h | 30 h | 36 h | Post clamp ^p | 48 h | 72 h | 96 h | 120 h | 168 h | | | |
| Urine Drug Screen (UDS) ^j | X | X | | | | | | | | | | | | | | | | | | | | | |
| Breath Alcohol Assessment | X | X | | | | | | | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen (per site SOP) | X | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Genetic Analysis ^k | | | X | | | | | | | | | | | | | | | | | | | | |
| Blood for Glucose Analysis ⁿ | X | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Non-Esterified Fatty Acids (NEFA) | | | X | | X | X | | X | X | X | | X | | | | | | | | | | | |
| Blood for Glycerol | | | X | | X | X | | X | X | X | | X | | | | | | | | | | | |
| Serum Ketones (β-hydroxybutyrate) | | | X | | | X | | | | X | | X | | | | | | | | | | | |
| Blood for Serum C-peptide | | | X | | X | X | | X | X | X | | X | | | | | | | | | | | |
| Blood for Serum Insulin | | | X | | | | | | | | | | | | | | | | | | | | |
| Blood for Serum Anti-MK-1092 and Anti-Glargine (Anti-Insulin) Antibody/Immunogenicity Assay | | | X | | | | | | | | | | | | | | | | | | X | X ^r | |
| Pharmacokinetics Evaluations | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-1092 and/or Metabolites assay and Glargine ^{l,m} | | | X | ----- | X | | | | | | | | | | | | | | | | X | X | |
| Pharmacodynamic Evaluations | | | | | | | | | | | | | | | | | | | | | | | |
| Euglycemic Clamp/ Infusion of Glucose ⁿ | | | | X | ----- | X | | | | | | | | | | | | | | | | | |
| Blood for Glucose Bedside Analysis ^o | | | X | ----- | X | | | | | | | | | | | | | | | | | | |

Scr = Screening; D = Study Day

- All subjects will participate in only 1 Panel.
- Screening should be done within 30 days of Day 1.
- Weight obtained at baseline (Day -1) will be used for determining amount of drug to be administered.
- All ECGs will be obtained in triplicate at least 1-2 min apart. Prior to each panel, predose ECGs will be obtained within 1-2 hr prior to dosing. The median of these measurements will be used as the baseline. During the infusion period post baseline ECG measurements will be taken at 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr and 36 hr. Measurements will also be collected at Post clamp, 48 hr and Post Trial (Day 14).
- At screening, the median of 3 measurements taken within a 10-min period (all 3 sets completed within 10 min) will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator. Prior to each period, HR and BP will be triplicate measurements obtained at least 1-2 min apart within approximately 60 min of dosing MK-1092/glargine. The median of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements. Post-dose vital sign assessments will be done at 30 min (0.5 hr), 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr, and 36 hr. Measurements will also be collected at 48 hr and Post Trial (Day 14).

- f. Study drug will be administered at Time 0.
- g. All adverse experiences (including serious adverse events) will be reported from the signing of informed consent through Day 33 (5 days from Day 28) for randomized subjects only. If a subject is required to return for additional post-trial visits for the continued assessment of ADAs/AIAs after Day 28 (+/- 3 days), a subsequent phone call should be made to the subject 5 (+2) days after the last protocol-specified procedure to determine if any adverse events have occurred since the previous contact for the assessment of AEs. Refer to Section 7.2 for pre-randomization/allocation AE/SAE reporting requirements.
- h. Injection site local tolerability assessment will be recorded as an adverse experience (AE) if any reactions are identified.
- i. For postmenopausal females without menses for at least 1 year.
- j. Screening UDS is mandatory, any additional UDS are conducted per site SOP
- k. 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.
- l. Leftover main study plasma will be stored for future biomedical research if the subject consents to future biomedical research.
- m. Blood for MK-1092 and glargine PK assay will be collected at the following timepoints -15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 540, 720, 1080, 1440 min, 48 hr, 72 hr, 96 hr, 120 hr and 168 hr following start of injection (i.e. - 15 min, 10 min, 30 min, 1.0 hr, 1.5 hr, 2.0 hr, 3.0 hr, 4.0 hr, 6.0 hr, 9.0 hr, 12 hr, 18 hr, 24 hr, 2d, 3d, 4d, 5d and 7d after SC dose). Blood will also be collected at Post-trial (Day 14 and Day 28). Exploratory analysis for MK-1092 metabolites may be performed. A sample will also be collected at Post clamp. Note that subjects will have only one (1) sample collected for MK-1092 and glargine PK at each time point and this sample will be processed and shipped to the appropriate laboratory for the respective PK assay (MK-1092 PK or glargine PK) by the unblinded lab personnel.
- n. 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 hr noted above.
- o. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and ~every 1 to 5 min. If necessary, collection may be performed more frequently at investigator's discretion. Bedside glucose analysis will continue at the discretion of the investigator and will be dependent on the duration of the clamp procedure. The duration of bedside glucose analysis may be shorter or longer than the 24 hr noted above. Additional glucose measurements will be assessed using Yellow Springs Instrument (YSI) per the Study Operations Manual and site SOP.
- p. Post-clamp procedures are to be performed shortly after the completion of the clamp (up to +10 mins), unless the clamp is concluded within 30 min of a previous collection time.
- q. Discharge should occur at a minimum of 48 hr after the start of the euglycemic clamp at the discretion of the investigator, post subject evaluation. After the end of the clamp procedures subjects may engage in normal activities, and will not be fasted. Subjects are discharged on Day 3, but return to the CRU on Days 4, 5, 6, 8, 14 and 28 for PK draws.
- r. If a subject has a positive drug-induced ADA/AIA titer at Day 28 follow-up visit, an additional sample will be drawn on Day 56 (+/- 5 days); additional sampling may be required (see Section 7.1.5.3 for more details).
- s. VS measurements prior to and including 6.0 hr may be collected +/- 15 min from the timepoint. The VS measurement after 6.0 hr may be collected +/- 30 min from the timepoint.
- t. Post-trial visits will be conducted Day 14 (+/-2) and Day 28 (+/- 3).
- u. To assess inclusion criterion 6 for healthy adult subjects, fasting blood glucose will be assessed following a minimum of an 8-hour fast using the point-of-care glucose analyzer (e.g. GlucoScout or YSI).

6.2 Part 2 (SC MK-1092 + IV Humalog in Healthy Adult Subjects)

| | Scr ^b | Treatment Panel ^a | | | | | | | | | | | | | | | | | | | Post-trial (Day 14 +/- 2 days) ^t | Post-trial (Day 28 +/- 3 days) ^t | | | | |
|--|------------------|------------------------------|----------|----|-----|-----|-----|-----|-----|----------------|------|------|------|------|------|-------------------------|----------------|------|------|-------|---|---|-------|----|---|--|
| | | D-1 | Pre-dose | D1 | | | | | | | | | D2 | | | | | D3 | D4 | D5 | | | D6 | D8 | | |
| | | | | 0 | 1 h | 2 h | 4 h | 6 h | 9 h | 12 h | 15 h | 18 h | 24 h | 30 h | 36 h | Post clamp ^p | 48 h | 72 h | 96 h | 120 h | | | 168 h | | | |
| 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 | X | | | | | | | | | | | | | | | | | | | | | | X | X | |
| Admission to the Unit | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Discharge from the Unit | | | | | | | | | | | | | | | | | | | | | | | | | | |
| 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 ^p | X | | | | | | | X | |
| Semi-Recumbent Vital Signs (heart rate (HR), blood pressure (BP)) ^{e,s} | X | | X | | | | | | X | X | | | X | X | X | X | | X | | | | | | | X | |
| Vital Signs (respiratory rate, oral/temporal/tympanic temperature) ^s | X | | X | | X | | X | X | | | | | | | | | | X | | | | | | | X | |
| MK-1092 Administration ^f | | | X | | | | | | | | | | | | | | | | | | | | | | | |
| Humalog Administration | | | | | | | | | X | X ^v | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring ^g | X | | | | | | | | | | | | | | | | | | | | | | | | X | |
| Injection site local tolerability assessment ^h | | | X | X | X | X | X | X | X | X | | | X | | X | | | X | | | | | | | | |
| Laboratory Procedures/Assessments | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematology | X | X | | | | | | | | | | | X | | | X ^p | | | | | | | | X | X | |
| Urinalysis | X | X | | | | | | | | | | | X | | | X ^p | | | | | | | X | X | | |
| Chemistry | X | X | | | | | | | | | | | X | | | X ^p | | | | | | | X | X | | |
| Serum Follicle Stimulating Hormone (FSH) ⁱ | X | | | | | | | | | | | | | | | | | | | | | | | | | |

Scr = Screening; D = Study Day

- a. There is only one panel in this Part. Subjects will not participate in other parts of the study.
- b. Screening should be done within 30 days of Day 1.
- c. 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 min apart. Prior to each panel, predose ECGs will be obtained within 1-2 hr prior to dosing. The median of these measurements will be used as the baseline. During the infusion period post baseline ECG measurements will be taken at 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr and 36 hr. Measurements will also be collected at Post clamp, 48 hr and Post Trial (Day 14).
- e. At screening, the median of 3 measurements taken within a 10-min period (all 3 sets completed within 10 min) will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator. Prior to each period, HR and BP will be triplicate measurements obtained at least 1-2 min apart within approximately 60 min of dosing MK-1092. The median of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements. On the day of MK-1092 administration, post-dose Vital Sign assessments will be done at 30 min (0.5 h), 60 min (1.0 h), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr, and 36 hr. Measurements will also be collected at 48 hr and Post Trial (Day 14).
- f. Study drug will be administered at Time 0.
- g. All adverse experiences (including serious adverse events) will be reported from the signing of informed consent through Day 33 (5 days from Day 28) for randomized subjects only. If a subject is required to return for additional post-trial visits for the continued assessment of ADAs/AIAs after Day 28 (+/- 3 days), a subsequent phone call should be made to the subject 5 (+2) days after the last protocol-specified procedure to determine if any adverse events have occurred since the previous contact for the assessment of AEs. Refer to Section 7.2 for pre-randomization/allocation AE/SAE reporting requirements.
- h. Injection site local tolerability assessment will be recorded as an adverse experience (AE) if any reactions are identified.
- i. For postmenopausal females without menses for at least 1 year.
- j. Screening UDS is mandatory, any additional UDS are conducted per site SOP
- k. 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.
- l. Leftover main study plasma will be stored for future biomedical research, if the subject consents to future biomedical research.
- m. Blood for MK-1092 PK assay will be collected at the following timepoints-15 min (predose), 30, 60, 120, 240, 540, 720, 730, 740, 750, 780, 840, 900, 1440 min, 48 hr, 72 hr, 96 hr, 120 hr and 168 hr following start of injection (i.e. - 15 min, 30 min, 1.0 hr, 2.0 hr, 4.0 hr, 9.0 hr, 12 hr, 12 hr 10 min, 12 hr 20 min, 12.5 hr, 13 hr, 14 hr, 15 hr, 24 hr, 2d, 3d, 4d, 5d and 7d after SC dose). Blood will also be collected at Post-trial (Day 14 and Day 28). A sample will also be collected at Post clamp. Exploratory analysis for MK-1092 metabolites may be performed. Samples for Humalog will include -15 min (predose) relative to MK-1092 dosing and 720, 730, 740, 750, 780, 840, 900 and 1440 min post MK-1092 dosing. The exact timing of the PK timepoints for MK-1092 and Humalog may be adjusted by results of Part 1. Any adjustments will be noted in a Protocol Clarification Letter when determined, but the total number of samples will not change.
- n. 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 hr noted above.
- o. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and ~every 1 to 5 min. If necessary, collection may be performed more frequently at investigator's discretion. Bedside glucose analysis will continue at the discretion of the investigator and will be dependent on the duration of the clamp procedure. The duration of bedside glucose analysis may be shorter or longer than the 24 hours noted above. Additional glucose measurements will be assessed using Yellow Springs Instrument (YSI) per the Study Operations Manual and site SOP.
- p. Post-clamp procedures are to be performed shortly after the completion of the clamp (up to +10 min), unless the clamp is concluded within 30 min of a previous collection time.
- q. Discharge should occur at a minimum of 48 hours after the start of the euglycemic clamp at the discretion of the investigator, post subject evaluation. After the end of the clamp procedures subjects may engage in normal activities, and will not be fasted. Subjects are discharged on Day 3, but return to the CRU on Day 4, 5, 6, 8, 14 and 28 for PK draws.

- r. If a subject has a positive drug-induced ADA/AIA titer at Day 28 follow-up visit, an additional sample will be drawn on Day 56 (+/- 5 days); additional sampling may be required (see Section 7.1.5.3 for more details).
- s. VS measurements prior to and including 6.0 hr may be collected +/- 15 min from the timepoint. The VS measurement after 6.0 hr may be collected +/- 30 minutes from the timepoint.
- t. Post-trial visits will be conducted Day 14 (+/-2) and Day 28 (+/- 3).
- u. To assess inclusion criterion 6 for healthy adult subjects, fasting blood glucose will be assessed following a minimum of an 8-hour fast using the point-of-care glucose analyzer (e.g. GlucoScout or YSI).
- v. IV Humalog will be infused over three hours, starting ~12 hr after SC administration of MK-1092, a time at which MK-1092 is anticipated to have a glycemic effect. The actual start time of Humalog infusion may be altered based on data from Part 1 and will be communicated to the site by a Protocol Clarification Letter prior to dosing.

6.3 Part 3 (MK-1092/Glargine Subcutaneous Injection in Adult T1DM Subjects)

| | | All Panels ^a | | | | | | | | | | | | | | | | | | | | Post-trial (Day 14 +/- 2 days) ^y | Post-trial (Day 28 +/- 3 days) ^y | | |
|---|------------------|-------------------------|---------|---------|---------|------------------|-------|--------|--------|--------|--------|--------|---------|---------|---------|---------|---------|----------------------------|----------------|---------|---------|---|---|-------|---|
| | Scr ^b | Washout Period | | | | Treatment Period | | | | | | | | | | | | | | | | | | | |
| | | D -4 | D -3 | D -2 | D -1 | D1 | | | | | D2 | | | | | D3 | D4 | D5 | D6 | D8 | | | | | |
| | | | | | | Predose | 0 | 1 h | 2 h | 4 h | 6 h | 9 h | 12 h | 18 h | 24 h | 30 h | 36 h | Post clamp ^q | 48 h | 72 h | 96 h | 120 h | 168 h | | |
| 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 | X | | | | | | | | | | | | | | | | | | | | | | | X |
| Admission to the Unit | | X | | | | | | | | | | | | | | | | | | | | | | | 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 ^q | X | | | | | | X |
| Semi-Recumbent Vital Signs (heart rate (HR), blood pressure(BP)) ^{e,t} | X | | | | | X | ----- | X | | | | X | X | X | X | X | X | | X | | | | | | X |
| Vital Signs (respiratory rate, oral/temporal/tympanic temperature) ^l | X | | | | | X | | X | | X | X | | | | | | | | X | | | | | | X |
| MK-1092/Glargine Administration ^f | | | | | | | X | | | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring ^g | X | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | ----- | X |
| Injection site local tolerability assessment ^h | | | | | | X | X | X | X | X | X | X | X | | X | | X | | X | | | | | | |
| Laboratory Procedures/Assessments | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hematology | X | | | | X | | | | | | | | | | X | | | X ^q | | | | | X | | X |
| Urinalysis | X | | | | X | | | | | | | | | | X | | | X ^q | | | | | X | | X |
| Chemistry | X | | | | X | | | | | | | | | | X | | | X ^q | | | | | X | | X |
| Serum Follicle Stimulating Hormone (FSH) ⁱ | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Urine Drug Screen (UDS) ^j | X | X | | | | | | | | | | | | | | | | | | | | | | | |
| Breath Alcohol Assessment | X | X | | | | | | | | | | | | | | | | | | | | | | | |

| | | All Panels ^a | | | | | | | | | | | | | | | | | | | | | | | Post-trial (Day 14 +/- 2 days) ^v | Post-trial (Day 28 +/- 3 days) ^v | |
|--|------------------|-------------------------|---------|---------|---------|------------------|-------|-------|---|---|---|---|----|----|----|----|----|-------------------------|----|----|----|-----|-----|---|---|---|----------------|
| | Scr ^b | Washout Period | | | | Treatment Period | | | | | | | | | | | | | | | | | | | | | |
| | | D -4 | D -3 | D -2 | D -1 | D1 | | | | | | | | D2 | | | | D3 | D4 | D5 | D6 | D8 | | | | | |
| | | | | | | Pre-dose | 0 | 1 | 2 | 4 | 6 | 9 | 12 | 18 | 24 | 30 | 36 | Post clamp ^q | 48 | 72 | 96 | 120 | 168 | | | | |
| HIV/Hepatitis Screen (per site SOP) | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Genetic Analysis ^k | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Blood for Glucose Analysis ^w | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for HbA1c Analysis | X | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Non-Esterified Fatty Acids (NEFA) | | | | | | X | | | X | X | | X | X | X | | X | | | | | | | | | | | |
| Blood for Glycerol | | | | | | X | | | X | X | | X | X | X | | X | | | | | | | | | | | |
| Serum Ketones (β-hydroxybutyrate) | | | | | | X | | | | | X | | | | X | | X | | | | | | | | | | |
| Blood for Serum C-peptide | X ^w | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Serum Anti-MK-1092 and Anti-Glargine (Anti-Insulin) Antibody/ Immunogenicity Assay | | | | | | X | | | | | | | | | | | | | | | | | | | | X | X ^s |
| Pharmacokinetics Evaluations | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-1092 and/or Metabolites assay and Glargine ^{l,m} | | | | | | X | ----- | X | | | | | | | | | | | X | X | X | X | X | X | X | X | X |
| Pharmacodynamic Evaluations | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| IV infusion of insulin ⁿ | | | | | | X | ----- | X | | | | | | | | | | | | | | | | | | | |
| IV infusion of dextrose ⁿ | | | | | | X | | | | | | | | | | | | | | | | | | | | | |
| Euglycemic Clamp/ Infusion of Glucose ^o | | | | | | | X | ----- | X | | | | | | | | | | | | | | | | | | |
| Blood for Glucose Bedside Analysis ^p | | | | | | X | ----- | X | | | | | | | | | | | | | | | | | | | |
| Fingerstick Glucose Testing ^u | | X | X | X | X | | | | | | | | | | | | | X | X | | | | | | | | |
| Continuous Glucose Monitoring | | X | ----- | X | | | | | | | | | | | | | | | X | | | | | | | | |

Scr = Screening; D = Study Day

- a. All subjects will participate in only 1 Panel.
- b. Screening should be done within 30 days of Day 1.
- c. 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 min apart. Prior to each panel, predose ECGs will be obtained within 1-2 hr prior to dosing. The median of these measurements will be used as the baseline. During the infusion period post baseline ECG measurements will be taken at 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr and 36 hr. Measurements will also be collected at Post clamp, 48 hr and Post Trial (Day 14).
- e. At screening, the median of 3 measurements taken within a 10-min period (all 3 sets completed within 10 min) will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator. Prior to each period, HR and BP will be triplicate measurements obtained at least 1-2 min apart within approximately 60 min of dosing MK-1092/glargine. The median of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements. On the day of MK-1092/glargine administration, post-dose Vital Sign assessments will be done at 30 min (0.5 h), 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr, and 36 hr. Measurements will also be collected at 48 hr and Post Trial (Day 14).
- f. Study drug will be administered at Time 0.
- g. All adverse experiences (including serious adverse events) will be reported from the signing of informed consent through Day 33 (5 days from Day 28) for randomized subjects only. If a subject is required to return for additional post-trial visits for the continued assessment of ADAs/AIAs after Day 28 (+/- 3 days), a subsequent phone call should be made to the subject 5 (+2) days after the last protocol-specified procedure to determine if any adverse events have occurred since the previous contact for the assessment of AEs. Refer to Section 7.2 for pre-randomization/allocation AE/SAE reporting requirements.
- h. Injection site local tolerability assessment will be recorded as an AE if any reactions are identified.
- i. For postmenopausal females without menses for at least 1 year.
- j. Screening UDS is mandatory, any additional UDS are conducted per site SOP
- k. 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.
- l. Leftover main study plasma will be stored for future biomedical research, if the subject consents to future biomedical research.
- m. Blood for MK-1092 and glargine PK assay will be collected at the following timepoints-15 min (predose), 10, 30, 60, 90, 120, 180, 240, 360, 540, 720, 1080, 1440 min, 48 hr, 72 hr, 96 hr, 120 hr and 168 hr following start of injection (i.e. - 15 min, 10 min, 30 min, 1.0 hr, 1.5 hr, 2.0 hr, 3.0 hr, 4.0 hr, 6.0 hr, 9.0 hr, 12 hr, 18 hr, 24 hr, 2d, 3d, 4d, 5d and 7d after SC. dose). Blood will also be collected at Post-trial (Day 14 and Day 28). Exploratory analysis for MK-1092 metabolites may be performed. A sample will also be collected at Post clamp. The exact timing of the PK timepoints for MK-1092/glargine may be adjusted by results of Part 1. Any adjustments will be noted in a Protocol Clarification Letter when determined, but the total number of samples will not change. Note that subjects will have only one (1) sample collected for MK-1092 and glargine PK at each time point and this sample will be processed and shipped to the appropriate laboratory for the respective PK assay (MK-1092 PK or glargine PK) by the unblinded lab personnel.
- n. IV infusion of insulin and dextrose, as needed, will begin at the start of the 8 hr overnight fast on Day -1. IV insulin will be weaned following SC dosing with MK-1092/glargine in order to maintain glucose concentrations at ~100 mg/dL.
- o. 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 hr noted above.
- p. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and ~every 1 to 5 min. If necessary, collection may be performed more frequently at investigator's discretion. Bedside glucose analysis will continue at the discretion of the investigator and will be dependent on the duration of the clamp procedure. The duration of bedside glucose analysis may be shorter or longer than the 24 hr noted above. Additional glucose measurements will be assessed using Yellow Springs Instrument (YSI) per the Study Operations Manual and site SOP.

- q. Post-clamp procedures are to be performed shortly after the completion of the clamp (up to +10 min), unless the clamp is concluded within 30 min of a previous collection time.
- r. Discharge should occur at a minimum of 48 hr after the start of the euglycemic clamp at the discretion of the investigator, post subject evaluation. After the end of clamp procedures, subjects may engage in normal activities, and will not be fasted. Subjects are discharged on Day 3, but return to the CRU on Day 4, 5, 6, 8, 14, and 28 for PK draws.
- s. If a subject has a positive drug-induced ADA/AIA titer at the Day 28 follow-up visit, an additional sample will be drawn on Day 56 (+/- 5 days); additional sampling may be required (see Section 7.1.5.3 for more details).
- t. VS measurements prior to and including 6.0 hr may be collected +/- 15 min from the timepoint. The VS measurement after 6.0 hr may be collected +/- 30 min from the timepoint.
- u. Glucose assessments (from fingersticks and/or CGM) should occur before meals, before bedtime (~11:00 PM), and as needed overnight from admission to the CRU until Day 3. If a subject remains domiciled in the CRU past Day 3, glucose assessments should occur at the discretion of the investigator until the time of discharge.
- v. Post-trial visits will be conducted Day 14 (+/-2) and Day 28 (+/- 3) after the last dose of trial drug.
- w. C-peptide is to be measured at screening unless a documented measurement was obtained within 24 weeks prior to screening. To assess inclusion criteria 7, C-peptide must be measured when plasma glucose is >90 mg/dL (> 5.0 mM). If necessary, the subject may consume carbohydrates to raise plasma glucose over 90 mg/dL (5.0 mM) as measured by point of care analyzer (YSI or GlucoScout) prior to drawing blood for C-peptide. This may be repeated by the site as needed to ensure C-peptide is assessed when plasma glucose concentration is >90 mg/dL (> 5.0 mM).

6.4 Part 4 (MK-1092/Glargine Subcutaneous Injection in Adult T2DM Subjects)

| All Periods (Periods 1 – 3) ^a | | | | | | | | | | | | | | | | | | | | | | |
|---|------------------|----------------|---------|---------|---------|------------------|--------|--------|--------|--------|--------|--------|---------|----------------|---------|---------|---------|----------------|---------------|--|--|---------------|
| | Scr ^b | Washout Period | | | | Treatment Period | | | | | | | | | | | | | | Post-trial (Day 14 +/- 2 days) ^v | Post-trial (Day 28 +/- 3 days) ^v | |
| | | D -4 | D -3 | D -2 | D -1 | D1 | | | | | | | D2 | | | | | D3 48 h | D4 72 h | | | D5 96 h |
| | | | | | | Predose | 0 h | 1 h | 2 h | 4 h | 6 h | 9 h | 12 h | 18 h | 24 h | 30 h | 36 h | | | | | |
| 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 | X | | | | | | | | | | | | | | | | | | X | | |
| Admission to the Unit | | X | | | | | | | | | | | | | | | | | | | | |
| Discharge from the Unit | | | | | | | | | | | | | | | | | | X ^f | | | | |
| 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 ^q | X | | | | | X | | |
| Semi-Recumbent Vital Signs (heart rate (HR), blood pressure(BP)) ^{e,t} | X | | | | | X-----X | X | X | X | X | X | X | X | X | | | | | | X | | |
| Vital Signs (respiratory rate, oral/temporal/tympanic temperature) ^t | X | | | | | X | X | X | X | | | | | | X | | | | | X | | |
| MK-1092/Glargine Administration ^t | | | | | | X | | | | | | | | | | | | | | | | |
| Adverse Events Monitoring ^g | X | -----X | | | | | | | | | | | | | | | | | | | | |
| Injection site local tolerability assessment ^h | | | | | | X | X | X | X | X | X | X | X | X | X | | X | | | | X | |
| Laboratory Procedures/Assessments | | | | | | | | | | | | | | | | | | | | | | |
| Hematology | X | | | | X | | | | | | | | | | X | | | | | X | | |
| Urinalysis | X | | | | X | | | | | | | | | | X | | | | | X | | |
| Chemistry | X | | | | X | | | | | | | | | | X | | | | | X | | |
| Serum Follicle Stimulating Hormone (FSH) ⁱ | X | | | | | | | | | | | | | | | | | | | | | |
| Urine Drug Screen (UDS) ^j | X | X | | | | | | | | | | | | | | | | | | | | |
| Breath Alcohol Assessment | X | X | | | | | | | | | | | | | | | | | | | | |
| HIV/Hepatitis Screen (per site) | X | | | | | | | | | | | | | | | | | | | | | |

| All Periods (Periods 1 – 3) ^a | | | | | | | | | | | | | | | | | | | | | | | | |
|--|------------------|----------------|---------|---------|---------|------------------|---------|--------|--------|--------|--------|--------|---------|---------|---------|---------|---------|----------------------------|---------|---------|--|--|---------|----------------|
| | Scr ^b | Washout Period | | | | Treatment Period | | | | | | | | | | | | | | | Post-trial (Day 14 +/- 2 days) ^y | Post-trial (Day 28 +/- 3 days) ^y | | |
| | | D -4 | D -3 | D -2 | D -1 | D1 | | | | | | | D2 | | | | D3 | D4 | D5 | | | | | |
| | | | | | | Pre-dose | 0 h | 1 h | 2 h | 4 h | 6 h | 9 h | 12 h | 18 h | 24 h | 30 h | 36 h | Post clamp ^q | 48 h | 72 h | | | 96 h | |
| SOP) | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Genetic Analysis ^k | | | | | | X ^w | | | | | | | | | | | | | | | | | | |
| Blood for HbA1c Analysis | X | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Non-Esterified Fatty Acids (NEFA) ^x | | | | | | X | | X | X | X | | | X | | X | | | | | | | | | |
| Blood for Glycerol ^x | | | | | | X | | X | X | X | | | X | | X | | | | | | | | | |
| Serum Ketones (β-hydroxybutyrate) ^x | | | | | | X | | | X | | | | X | | X | | | | | | | | | |
| Serum C-peptide ^x | | | | | | X | | X | X | X | | | X | | X | | | | | | | | | |
| Blood for Serum Anti-MK-1092 and Anti-Glargine (Anti-Insulin) Antibody/ Immunogenicity Assay | | | | | | X ^w | | | | | | | | | | | | | | | | | X | X ^s |
| Pharmacokinetics Evaluations | | | | | | | | | | | | | | | | | | | | | | | | |
| Blood for Plasma MK-1092 and/or Metabolites assay and Glargine ^{l,m} | | | | | | X-----X | | | | | | | | | | | | | X | X | X | X | X | X |
| Pharmacodynamic Evaluations | | | | | | | | | | | | | | | | | | | | | | | | |
| IV infusion of insulin ⁿ | | | | | | X-----X | | | | | | | | | | | | | | | | | | |
| IV infusion of dextrose ⁿ | | | | | | X | | | | | | | | | | | | | | | | | | |
| Euglycemic Clamp/ Infusion of Glucose ^o | | | | | | | X-----X | | | | | | | | | | | | | | | | | |
| Blood for Glucose Bedside Analysis ^p | | | | | | X-----X | | | | | | | | | | | | | | | | | | |
| Fingerstick Glucose Testing ^u | | X | X | X | X | | | | | | | | | | | | | | X | X | | | | |
| Continuous Glucose Monitoring | | X-----X | | | | | | | | | | | | | | | | | | | | | | |

Scr = Screening; D = Study Day

- a. Subjects will participate in all periods (Periods 1 – 3).
- b. Screening should be done within 30 days of Day 1 in Period 1.
- c. Weight obtained at baseline (Day -1) in each period will be used for determining amount of drug to be administered for that period.
- d. All ECGs will be obtained in triplicate at least 1-2 min apart. Prior to each period, predose ECGs will be obtained within 1-2 hr prior to dosing. The median of these measurements will be used as the baseline. During the infusion period post baseline ECG measurements will be taken at 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr and 36 hr. Measurements will also be collected at Post clamp, 48 hr and Post Trial (Day 14 relative to the last period dosed).
- e. At screening, the median of 3 measurements taken within a 10-min period (all 3 sets completed within 10 min) will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator. Prior to each period, HR and BP will be triplicate measurements obtained at least 1-2 min apart within approximately 60 min of dosing MK-1092/glargine. The median of these measurements will be used as the baseline. Post-dose vital sign measurements will be single measurements. On the day of MK-1092/glargine administration, post-dose Vital Sign assessments will be done at 30 min (0.5 h), 60 min (1.0 hr), 180 min (3.0 hr), 360 min (6.0 hr), 9.0 hr, 12 hr, 18 hr, 24 hr, 30 hr, and 36 hr. Measurements will also be collected at 48 hr and Post Trial (Day 14 relative to the last period dosed).
- f. Study drug will be administered at Time 0 within each period.
- g. All adverse experiences (including serious adverse events) will be reported from the signing of informed consent through Day 33 (5 days from Day 28 relative to the last period dosed) for randomized subjects only. If a subject is required to return for additional post-trial visits for the continued assessment of ADAs/AIAs after Day 28 (+/- 3 days), a subsequent phone call should be made to the subject 5 (+2) days after the last protocol-specified procedure to determine if any adverse events have occurred since the previous contact for the assessment of AEs. Refer to Section 7.2 for pre-randomization/allocation AE/SAE reporting requirements.
- h. Injection site local tolerability assessment will be recorded as an AE if any reactions are identified.
- i. For postmenopausal females without menses for at least 1 year.
- j. Screening UDS is mandatory, any additional UDS are conducted per site SOP
- k. 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.
- l. Leftover main study plasma will be stored for future biomedical research, if the subject consents to future biomedical research.
- m. Blood for MK-1092 and glargine PK assay will be collected at the following timepoints within Periods 1 and 2: -15 min (predose), 30, 60, 120, 180, 240, 360, 540, 720, 1080, 1440 min, 48 hr, 72 hr, and 96 hr, following start of injection (i.e. - 15 min, 30 min, 1.0 hr, 2.0 hr, 3.0 hr, 4.0 hr, 6.0 hr, 9.0 hr, 12 hr, 18 hr, 24 hr, 2d, 3d, and 4d after SC dose). Blood for MK-1092 and glargine PK assay will be collected at the following timepoints within Period 3 only: -15 min (predose), 60, 180, 240, 360, 540, 720, 1080, 1440 min, 48 hr, and 72 hr, following start of injection (i.e. - 15 min, 1.0 hr, 3.0 hr, 4.0 hr, 6.0 hr, 9.0 hr, 12 hr, 18 hr, 24 hr, 2d, and 3d after SC dose). Blood will also be collected at Post-trial (Day 14 and Day 28 relative to the last period dosed). Exploratory analysis for MK-1092 metabolites may be performed. Any adjustments will be noted in a Protocol Clarification Letter when determined, but the total number of samples will not change. Note that subjects will have only one (1) sample collected for MK-1092 and glargine PK at each time point and this sample will be processed and shipped to the appropriate laboratory for the respective PK assay (MK-1092 PK or glargine PK) by the unblinded lab personnel.
- n. IV infusion of insulin and dextrose, as needed, will begin at the start of the 8 hr overnight fast on Day -1 within each period. IV insulin will be weaned following SC dosing with MK-1092/glargine in order to maintain glucose concentrations at ~100 mg/dL.
- o. 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 hr noted above.
- p. Plasma for bedside glucose analysis should be collected at approximately -5 min predose and ~every 1 to 5 min. If necessary, collection may be performed more frequently at investigator's discretion. Bedside glucose analysis will continue at the discretion of the investigator and will be dependent on the duration of the clamp procedure. The duration of bedside glucose analysis may be shorter or longer than the 24 hr noted above. Additional glucose measurements will be assessed using Yellow Springs Instrument (YSI) per the Study Operations Manual and site SOP.

- q. Post-clamp procedures are to be performed shortly after the completion of the clamp (up to +10 min), unless the clamp is concluded within 30 min of a previous collection time.
- r. Discharge should occur at a minimum of 48 hr after the start of the euglycemic clamp in each period at the discretion of the investigator, post subject evaluation. After the end of the clamp procedures, subjects may engage in normal activities, and will not be fasted. Subjects are discharged on Day 3 of each period, at the discretion of the investigator, but will return to the CRU on Day 4 and 5 for PK draws. Subjects will also return to the clinic for the Day 14 and Day 28 post-trial visits relative to Day 1 of the last period dosed.
- s. If a subject has a positive drug-induced ADA/AIA titer at the Day 28 follow-up visit, an additional sample will be drawn on Day 56 (+/- 5 days) relative to Day 1 of the last period dosed; additional sampling may be required (see Section 7.1.5.3 for more details).
- t. VS measurements prior to and including 6.0 hr may be collected +/- 15 min from the timepoint. The VS measurement after 6.0 hr may be collected +/- 30 min from the timepoint.
- u. Glucose assessments (from fingersticks and/or CGM) should occur before meals, before bedtime (~11:00 PM), and as needed overnight from admission to CRU until Day 3. If a subject remains domiciled in the unit past Day 3, glucose assessments should occur at the discretion of the investigator until the time of discharge.
- v. Post-trial visits will be conducted Day 14 (+/-2) and Day 28 (+/- 3) after Day 1 of the last period dosed.
- w. Blood for Genetic Analysis sample and predose ADA/AIA sample are to be collected predose on Day 1 of Period 1 only.
- x. Blood for NEFA, C-peptide, glycerol and ketones will be collected in Period 1 and Period 2 at the time points specified in the trial flow chart. Blood for NEFA, C-peptide, glycerol, and ketones will be collected in Period 3 only at the following time points: predose and 24 hr postdose only.

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 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 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 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.

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 subject's shoes off, jacket or coat removed. The subject's weight is to be documented in kilograms (kg), to the nearest 0.1 kg and the subject's height is to be documented in meters, to the nearest 0.01 meter (0.01 meter = 1 centimeter, cm).

Body Mass Index (BMI)

BMI equals a person's weight in kilograms divided by height in meters squared. (BMI=kg/m²).

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 position 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.

In all treatment periods, all ECGs will be obtained in triplicate, and the median of all parameters will be calculated. There should be ~1-2 minute intervals between ECG measurements. Predose ECGs will be obtained in triplicate at least 1-2 minutes apart within 1-2 hours prior to dosing MK-1092/glargine. The median 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 median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the 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 or designee to be available as needed to review ECG tracings with significant abnormalities observed at any point during the trial.

Body Temperature

Body temperature will be measured with an oral, temporal artery, or tympanic thermometer. The same method (e.g., oral, temporal, or tympanic) 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 subject's arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

At screening, HR and BP will be triplicate measurements obtained within a 10-minute period (all 3 sets completed within 10 minutes) and the median of the three measurements will be used to assess for subject eligibility. This may be repeated on a second screening day at the discretion of the study investigator.

The predose (baseline) HR and BP will be triplicate measurements obtained at least 1-2 minutes apart within 60 minutes of dosing with study drug (MK-1092/glargine). The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Post-dose vital sign measurements will be single measurements regardless of treatment assignment.

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 blood glucose target in the euglycemic range (~5% below fasting level for healthy adult subjects and ~100 mg/dL for adult subjects with T1DM and adult subjects with T2DM). The clamp will be maintained after SC injection of MK-1092/glargine in Parts 1, 3, and 4, and after SC injection MK-1092 followed by Humalog infusion Part 2, to characterize washout of the PD effect and to ensure safety. For healthy adult subjects (Part 1 and 2), the clamp will be discontinued at the discretion of the investigator when the GIR appears stable near 0 mg/kg/min. For adult subjects with T1DM (Part 3) and adult subjects with T2DM (Part 4), the clamp will be completed when blood glucose is >150 mg/dL for 30 minutes in the absence of exogenous glucose infusion or sooner at the discretion of the investigator; exogenous insulin will be given at this time if needed.

Blood 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 7](#).

Table 7 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|--|--|---|---|
| Hematocrit | Albumin | Blood | Follicle Stimulating Hormone (FSH) ^a |
| Hemoglobin | Alkaline phosphatase | Glucose | Urine Drug Screen (UDS) |
| Platelet count | Alanine aminotransferase (ALT) | Protein | Hepatitis B/C screening |
| WBC:(total and differentials) [†] | Aspartate aminotransferase (AST) | Specific gravity | HIV |
| | Bicarbonate | Microscopic exam, if abnormal results are noted | Breath alcohol assessment |
| | Calcium | Albumin ^c | C-peptide ^d |
| | Chloride | Creatinine ^c | Insulin |
| | Creatinine | | Nonesterified Fatty Acids (NEFA). Also known as Free Fatty Acids (FFA). |
| | Glucose | | Ketones (β -hydroxybutyrate) |
| | Potassium | | Glycerol |
| | Sodium | | HbA1c ^b |
| | Magnesium | | |
| | Total Bilirubin | | |
| | Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal | | |
| | Total protein | | |
| | Blood Urea Nitrogen | | |
| | Gamma-glutamyl transferase | | |
| <p>[†] BC (total and differential) includes: Absolute neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, and Absolute Basophils.</p> <p>a. Only to be conducted for female subjects</p> <p>b. Only to be conducted for subjects with type 1 diabetes mellitus (T1DM) and subjects with type 2 diabetes mellitus (T2DM)</p> <p>c. Only to be conducted at screening for subjects with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) who have not had an assessment within 12 months of screening.</p> <p>d. Only to be conducted at screening for subjects with type 1 diabetes mellitus (T1DM) in Part 3 and at select time points pre- and post-dose in normal healthy subjects in Parts 1 and 2 and in subjects with type 2 diabetes mellitus (T2DM) in Part 4.</p> | | | |

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. Testing for C-peptide can be conducted fasting or after ingestion of carbohydrates. Pre-dose laboratory safety tests (chemistry, hematology, urinalysis) procedures can be conducted up to 30 hours prior to dosing on Day -1, and must be reviewed. Predose (Day 1) C-peptide, insulin, NEFA, ketones and glycerol, if applicable, do not need to be reviewed prior to dosing on Day 1.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The decision as to which 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-1092

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 Humalog

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

7.1.3.2.4 Blood Collection for Blood Glucose (Bedside Analysis)

Ambient glucose concentrations from blood will be recorded frequently (approximately 5 minutes apart) by point-of-care assessment 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 and site SOP.

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

7.1.3.2.5 Blood Collection for Anti-MK-1092 and Anti-Insulin Antibody/Immunogenicity Assay

Serum samples will be collected to assess the presence of anti-MK-1092/anti-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-1092 and/or Metabolites assay or glargine
- Leftover main study plasma from Humalog assay

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) 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, 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. An additional follow-up phone call should be made to the subject on Day 33 (+ 2 days) to determine if any adverse events have occurred since the last contact. For Parts 1 – 3, Day 33 is relative to Day 1 in each panel. In Part 4, Day 33 is relative to Day 1 of the last period dosed prior to discontinuation. 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 (clinical.specimen.management@merck.com). 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.

7.1.4.3 Domiciling

Healthy adult subjects participating in Parts 1 and 2 will report to the clinical research unit (CRU) on Day -1 prior to the scheduled day of trial drug administration on Day 1. Subjects will remain in the unit until approximately 48 hours after the start of the euglycemic clamp. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

Adult subjects with T1DM participating in Part 3 will report to the CRU on Day -4 prior to the scheduled day of trial drug administration on Day 1. Subjects will be placed on continuous glucose monitoring (CGM) and started on a SC insulin pump to maintain glycemic control with an appropriate regimen of basal and bolus insulin during washout of pre-study insulin therapy. Subjects who are already using a SC insulin pump for treatment of T1DM may continue to use their own SC pump during the study at the discretion of the investigator; however the investigator may alter the basal and bolus settings or require the use of a site-provided SC insulin pump based on medical judgment. After completion of the euglycemic clamp, adult subjects with T1DM will eat and their pre-study insulin regimen will be restarted at the discretion of the investigator; however, they will continue to wear the CGM and use the insulin pump as needed until glycemic control has been re-established using the pre-study insulin therapy. Subjects will be discharged from site ~48 hours after the start of the clamp. The time of discharge may be dependent upon glycemic control being re-established after the euglycemic clamp and can be lengthened based on investigator discretion.

Following SC treatment, subjects will remain in the unit until approximately 48 hours after the start of the euglycemic clamp, when glucose levels are stable. Adult subjects with T1DM may continue to wear an insulin pump and CGM, even if these devices are not being used, until discharge or these devices may be removed prior to discharge based on the clinical judgement and discretion of the investigator. At the discretion of the investigator, subjects may be requested to remain in the CRU longer.

Adult subjects with T2DM participating in Part 4 will be admitted to the CRU on Day -4 prior to the scheduled day of trial drug administration on Day 1 in each period and placed on continuous glucose monitoring (CGM). For all subjects with insulin-requiring T2DM, a SC insulin pump will be started to maintain glycemic control with an appropriate regimen of basal and bolus insulin. Subjects with non-insulin-requiring T2DM will not be placed on SC insulin pump unless the investigator determines this to be necessary to maintain glycemic control during the admission.

Subjects who are already using a SC insulin pump for treatment of T2DM may continue to use their own SC pump during the study at the discretion of the investigator; however the investigator may alter the basal and bolus settings or require the use of a site-provided SC insulin pump based on medical judgment.

After completion of the euglycemic clamp, adult subjects with T2DM will eat and their pre-study anti-diabetic regimen will be started at the discretion of the investigator; however, they will continue to wear the CGM and use the insulin pump as needed until glycemic control has been re-established using the pre-study anti-diabetic therapy, including insulin if needed. Subjects will be discharged from site ~48 hours after the start of the clamp. The time of discharge may be dependent upon glycemic control being re-established after the euglycemic clamp and can be lengthened based on investigator discretion.

Following SC treatment, subjects will remain in the unit until approximately 48 hours after the start of the euglycemic clamp, when glucose levels are stable. Adult subjects with T2DM may continue to wear an insulin pump (if needed) and CGM, even if these devices are not being used, until discharge or these devices may be removed prior to discharge based on the clinical judgement and discretion of the investigator. 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, syringe/infusion pumps for administering glucose and study drugs, CGM, and insulin pump.

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 in Parts 1 – 3, or prior to Day 1 in Period 1 for Part 4, 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-1092 (Parts 1, 2, 3, and 4) or glargine (Parts 1, 3, and 4) will be administered as a one-time injection on Day 1 of each panel or period. Intravenous Humalog (Part 2) will be infused for 3 hours starting ~12 hours after the administration of SC MK-1092 on Day 1. The actual start time of Humalog infusion was confirmed based on data from Part 1 and was communicated to the site prior to dosing for Part 2.

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 (Parts 1 and 2), or protocol-defined target glucose (Parts 3 and 4), during the medication infusion 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 the clinic on Day 14 (+/- 2 days) in Part 1-3 or on Day 14 (+/- 2 days) of the last period dosed in Part 4 for a post-trial visit for end of trial safety assessments (e.g. physical exam, ECG, VS, lab safety tests and AE assessments) and for the assessment of anti-drug antibodies (ADA) and anti-insulin antibodies (AIA). Subjects will additionally be required to return to the clinic on Day 28 (+/- 3 days) in Parts 1-3 or on Day 28 (+/- 3 days) of the last period dosed in Part 4 for collection of samples for assessment of ADA and AIA. A follow-up phone call should be placed to the subject on Day 33 (+2 days) in Parts 1-3 or on Day 33 (+/- 2 days) of the last period dosed in Part 4 for the assessment of adverse experiences.

If a subject has a drug-induced positive ADA/AIA response at the Day 28 (+/- 3 days) visit, an additional sample will be drawn on Day 56 (+/- 5 days) in Parts 1-3 or on Day 56 (+/- 5 days) of the last period dosed in Part 4 after the completion of dosing. At the same time, fasting blood glucose will be assessed using point-of-care glucose analyzer (e.g. YSI) 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 subjects with detectable ADAs until one of the following occurs:

- a) subject no longer has detectable drug-induced ADAs/AIAs,
- b) Drug-induced ADAs/AIAs are persistent and stable (magnitude of response not significantly increasing) on 3 consecutive checks at Day 28, Day 56 and additional 3 month intervals, if needed

Fasting blood glucose will be assessed by point-of-care glucose analyzer (e.g. YSI) at each time a subject returns for drug-induced 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. If a post-trial visit for the continued assessment of ADAs/AIAs occurs after Day 28 (+/- 3 days), a subsequent phone call should be made to the subject 5 (+2 days) after the last protocol-specified procedure to determine if any adverse events have occurred since the previous contact for the assessment of AEs.

7.1.5.4 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the critical procedures, in order of priority, are the glucose clamp procedures followed by the blood sample collections for MK-1092 and glargine.

Blood collection and other procedures directly related to the execution of the euglycemic clamp procedure need to be completed as close to the exact timepoint as possible. In addition, at any post-dose time point, the blood sample for MK-1092 and for glargine need to be collected as close to the exact time point 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 8](#) below

Table 8 PK Collection Windows

| Parts 1, 2, 3 and 4 | |
|--|----------------------|
| PK collection (time post-dose in each panel or period) | PK Collection Window |
| 10 min to < 14 hr | +/- 5 min |
| 14 hr to 24 hr | +/- 10 min |
| > 24 hr to < 48 hr | +/- 30 min |
| ≥ 48 hr | +/- 2 hr |

- Predose standard safety evaluations:
 - Vital Signs: 60 min prior to dosing
 - ECG: 60 - 120 min prior to dosing
 - Laboratory safety tests & physical exam: 30 hr prior to dosing
- Postdose standard safety evaluations
 - Vital signs (up to and including 6 hrs post-dose): +/- 15 min
 - Vital signs (after 6 hrs post-dose): +/- 30 min
 - ECG, laboratory safety tests: +/- 30 min

- Pharmacodynamic or other protocol specific measurements, or modification to any of the above windows:
 - NEFA, glycerol, C-peptide, and endogenous insulin: +/- 30 min
 - ADA/AIA: +/- 6 hr

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

This is a Phase I assessment of MK-1092 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 or periods
- Entire period(s) or panel(s) may be omitted
- Decrease in the duration of trial drug administration (e.g., number of hours)
- 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 the number of PK sampling timepoints
- Modification of the PK/PD sample processing and shipping details based on newly available data

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 of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses in Parts 1 – 3. Up to an additional 100 mL of blood may be drawn for safety, pharmacokinetic, and/or pharmacodynamic analyses in Part 4. This

includes additional blood that may be required for Yellow Springs Instrument (YSI) blood glucose assessments during the clamp procedure for safety. 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.

Adverse events, serious adverse events, and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization, must be reported by investigator for randomized participants only or participants enrolled in a run-in phase, 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 Day 33 (5 days after Day 28), or 5 days after the last protocol-specified procedure if additional follow-up ADA/AIA assessment visits are required, all adverse events must be reported by the investigator. For Parts 1 – 3, Day 33 is relative to Day 1 in each panel. In Part 4, Day 33 is relative to Day 1 of the last period dosed. 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) that occurs during the trial.

Pregnancies and lactations that occur after 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 that occur from the time of treatment

allocation/randomization through Day 33 (5 days after Day 28) following cessation of Sponsor's product, or 5 days after the last protocol-specified procedure if additional follow-up ADA/AIA assessment visits are required, must be reported by the investigator. For Parts 1 – 3, Day 33 is relative to Day 1 in each panel. In Part 4, Day 33 is relative to Day 1 of the last period dosed. 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 Events 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 9](#) 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 Day 33 (5 days after Day 28), or 5 days after the last protocol-specified procedure if additional follow-up ADA/AIA assessment visits are required, 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). For Parts 1 – 3, Day 33 is relative to Day 1 in each panel. In Part 4, Day 33 is relative to Day 1 of the last period dosed.

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 Day 33 (5 days after Day 28) following cessation of treatment, or 5 days after the last protocol-specified procedure if additional follow-up ADA/AIA assessment visits are required, 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). For Parts 1 – 3, Day 33 is relative to Day 1 in each Panel. In Part 4, Day 33 is relative to Day 1 of the last period dosed.

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.

3. 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. Skin lesions resulting from contact reactions to ECG lead adhesives and/or medical tape should be reported as AEs but do not need to be reported as ECI.
 - 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 9](#). The investigator's assessment of causality is required for each adverse event. Refer to [Table 9](#) for instructions in evaluating adverse events.

Table 9 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 (All Study Parts):

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.

Pharmacodynamics:

Individual maximal GIR values (GIR_{max}) during the clamp of MK-1092 SC or glargine SC administered to adult subjects with T1DM based on LOESS smoothed data from Part 3 will be analyzed in a fixed effects model with treatment as fixed effect (i.e. glargine, MK-1092 Dose Level 1, MK-1092 Dose Level 2, etc.). Means and 95% confidence intervals of GIR_{max} for each treatment/dose will be calculated from the model. Similar analysis (based on a slightly different model) will be done using data from Part 4 (T2DM). To test the Part 3 primary hypothesis, the posterior probability that the true mean GIR_{max} level is within 1.5 and 4.5 mg/kg/min will be calculated for each MK-1092 dose using a non-informative prior. If this posterior probability exceeds 70% for at least one safe and well tolerated dose of MK-1092 SC then the primary research hypothesis for Part 3 will be supported. There is no formal hypothesis testing (based on GIR) associated with Part 4. Posterior probabilities may be provided, if necessary.

Individual maximal GIR values (GIR_{max}) during the clamp in Part 1 will be determined based on LOESS smoothed data. Model based (similar to Part 3) statistics such as means, 95% confidence intervals etc. will be provided for each treatment/dose.

Pharmacokinetics (All Study Parts):

Geometric means and 95% confidence intervals will be provided for C_{max}, AUC_{0-∞} and CL/F, if calculated for the given study part, following SC administration by treatment.

Individual values will be listed for each PK parameter by treatment and the additional following (non-model-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). Median, minimum and maximum will only be provided for T_{max}.

The details for exploratory analyses can be found in Section 8.6.

Power

Pharmacodynamics (GIR_{max}):

The calculations in Table 10 below assume a between subject standard deviation of 0.44 for GIR_{max}, as was observed following SC administration of another IRPA (MK-5160) in healthy adult subjects. It is assumed that the variability of MK-1092 is similar to that of the other IRPA and that the variability in healthy adult subjects is similar to that in adult subjects with T1DM. The table below represents the probability of supporting the primary pharmacodynamics hypothesis under different assumed true mean of GIR_{max} values.

Table 10 Probability of Supporting Primary PD Hypothesis

| Target GIR_{max} (mg/kg/min) | True GIR_{max} | Probability of Supporting Hypothesis |
|---|-------------------------------|---|
| (1.5, 4.5) | 1 | 0.03% |
| | 1.5 | 30.9% |
| | 2 | 98.7% |
| | 2.5 | 100% |
| | 3 | 100% |
| | 3.5 | 100% |
| | 4 | 98.6% |
| | 4.5 | 29.40% |
| 5 | 0.06% | |

The calculations above were based on an assumed GIR_{max} standard deviation of 0.44 as observed in MK-5160 SC in P001, N=6 per dose, a posterior probability threshold of 70%, and 10,000 simulations.

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

Hypothesis (Primary):

- (1) At a dose with sufficient safety, the mean GIR_{max} after single SC administration of MK-1092 in adult subjects with T1DM is between 1.5 and 4.5 mg/kg/min. (Part 3)

8.4 Analysis Endpoints

Primary:

Safety

The primary safety endpoints in this study will include all types of adverse events (AE), 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 blood glucose at each subjects' individual clamp target, following administration of MK-1092 SC or glargine SC. To assess the primary hypothesis in Part 3, the maximal GIR (GIR_{max}) required to maintain the blood glucose target following administration of MK-1092 SC based on LOESS smoothed data during the euglycemic clamp timeframe is of interest.

Secondary:

Pharmacokinetics

MK-1092 SC pharmacokinetic variables of interest include C_{max} , $AUC_{0-\infty}$, CL/F , T_{max} and apparent terminal $t_{1/2}$ of. Similar variables for glargine are also of interest.

Pharmacodynamics

The glucose infusion rate (GIR) required to maintain blood glucose at each subjects' individual clamp target, following administration of MK-1092 SC or glargine SC in Parts 1

and 4 is a secondary endpoint. Specifically, GIR_{max} of MK-1092 SC or glargine SC during the euglycemic clamp timeframe are of interest in Parts 1 and 4.

In addition, time-weighted average based on GIR [TWA(GIR): $AUC(0-t)$ based on GIR values divided by time (t); t= 24, 36 etc.] is also of interest.

Exploratory:

Pharmacodynamics

The glucose infusion rate (GIR) required to maintain blood glucose at each subjects' individual clamp target following administration of MK-1092 SC after the start of Humalog infusion in Part 2 is of interest. The GIR_{max} of MK-1092 after the start of Humalog infusion is of interest in Part 2.

The exploratory pharmacodynamic endpoints in this study also include free fatty acids (FFA; also termed non-esterified fatty acids or NEFA), glycerol and ketones (e.g. β -hydroxybutyrate).

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 (All Study Parts):

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.

Pharmacodynamics:

GIR (Part 3)

Individual maximal GIR_{max} during the euglycemic clamp timeframe following MK-1092 SC or glargine SC administered to adult subjects with T1DM based on LOESS smoothed data from Part 3 will be analyzed in a fixed effects model with an effect for treatment (i.e. glargine dose, MK-1092 Dose Level 1, MK-1092 Dose Level 2, etc). Means and 95% confidence intervals of GIR_{max} for each treatment/dose will be calculated from the model. To test the Part 3 primary hypothesis, the posterior probability that the true mean GIR_{max} level is within 1.5 and 4.5 mg/kg/min will be calculated for each MK-1092 dose using a non-informative prior. If this posterior probability exceeds 70% for at least one safe and well tolerated dose of MK-1092 SC then the primary research hypothesis for Part 3 will be supported.

Additionally, a non-linear mixed effects model-based analysis may be used to assess the PK/PD (i.e. concentration/GIR) relationship. The model for MK-1092 will be developed using data from Part 3. The model for glargine will be developed using data from Part 3 of the current study and available historical data.

Secondary

Pharmacodynamics:

GIR (Parts 1 & 4):

Individual maximal GIR values (GIR_{max}) during the clamp in Part 1 and Part 4 will be smoothed based on LOESS method.

Model based (similar to Part 3: fixed effect model) statistics such as means, 95% confidence intervals etc. will be provided for each treatment/dose in Part 1.

For Part 4, a linear mixed effects model containing a fixed effect for treatment (MK-1092, Glargine), a nested effect from subjects within treatment (subjects within treatment), an interaction between treatment and period (treatment by period: Period = Period 1, 2, 3) and a random effect due to subjects will be used. Kenward and Roger's method will be used to calculate the denominator degrees of freedom for the fixed effects. Model based statistics such as means, 95% confidence intervals etc. will be provided for each treatment/dose.

TWA(GIR) (Part 1, 3 and 4):

Time-weighted average based on GIR [TWA(GIR): $AUC(0-t)$ based on GIR values divided by time (t)] is also of interest. Model based (similar to GIR_{max} in Part 3) statistics such as

means, 95% confidence intervals etc. will be provided for each treatment/dose. AUC will be computed based on all observed GIR values.

Pharmacokinetics (All Study Parts):

Geometric means and 95% confidence intervals (non-model based) will be provided for C_{max}, AUC_{0-∞} and CL/F if calculated for the given study part, following SC administration by treatment.

Individual values will be listed for each PK parameter by treatment and the additional following (non-model-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 T_{max}, median, minimum and maximum will be provided.

Exploratory

Pharmacodynamics

GIR (Part 2):

Individual values for GIR_{max} based on LOESS smoothed data after the start of Humalog administration in Part 2 will be listed only. Descriptive statistics will be provided also.

Free Fatty Acids (FFA):

Individual change from baseline serum FFA values in all Parts except Part 2, where baseline is the predose value, following SC administration of MK-1092 or glargine will be summarized with descriptive statistics and plotted over time. Formal treatment comparisons (MK-1092 versus glargine) may also be performed if deemed necessary. FFA values for each subject in Part 2 will be listed only.

Glycerol:

Individual change from baseline glycerol values, where baseline is the predose value, will be analyzed in a similar fashion as FFA.

Ketones (β-hydroxybutyrate):

Individual change from baseline β-hydroxybutyrate values, where baseline is the predose value, will be analyzed in a similar fashion as FFA.

Pharmacokinetics (Part 2):

General PK profile for Humalog IV may be explored descriptively.

General:

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, nonnormality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

8.7 Multiplicity

Formal statistical testing with associated p-value cut-offs centered around controlling Type-I error rates will not be used in assessing the hypotheses; hence no multiplicity adjustment is required or proposed.

8.8 Sample Size and Power Calculations

Pharmacodynamics (GIR_{max}):

The calculations in Table 11 below assume a between subject standard deviation of 0.44 for GIR_{max} , as was observed following SC administration of another IRPA (MK-5160) in healthy adult subjects. It is assumed that the variability of MK-1092 is similar to that of the other IRPA and that the variability in healthy adult subjects is similar to that in adult subjects with T1DM. The table below represents the probability of supporting the primary pharmacodynamics hypothesis under different assumed true mean of GIR_{max} values.

Table 11 Probability of Supporting Primary PD Hypothesis

| Target GIR_{max} (mg/kg/min) | True GIR_{max} | Probability of Supporting Hypothesis |
|--|------------------------------------|---|
| (1.5, 4.5) | 1 | 0.03% |
| | 1.5 | 30.9% |
| | 2 | 98.7% |
| | 2.5 | 100% |
| | 3 | 100% |
| | 3.5 | 100% |
| | 4 | 98.6% |
| | 4.5 | 29.40% |
| | 5 | 0.06% |

The calculations above were based on an assumed GIR_{max} standard deviation of 0.44 as observed in MK-5160 SC in P001, N=6 per dose, a posterior probability threshold of 70%, and 10,000 simulations.

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 12](#).

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 12 Product Description

| Product Name & Potency | Dosage Form | Source/Additional Information |
|-----------------------------------|---|--------------------------------------|
| MK-1092, 20.0 mg/mL | Sterile Solution for Injection, 1.0 mL per vial | Supplied by Sponsor |

All supplies indicated in [Table 12](#) will be provided per the “Source/Additional Information” column depending on local country operational requirements.

Any commercially available product not included in [Table 12](#) 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

Part 2 of the trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Part 1, Part 3 and Part 4 of this trial are blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment allocation/randomization schedule for the trial to unblind subjects and to unmask treatment identity for this trial. 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] International Diabetes Federation. IDF diabetes atlas: seventh edition 2015 [Internet]. Brussels, BE: International Diabetes Federation; 2015. Available from:
http://www.indiaenvironmentportal.org.in/files/file/IDF_Atlas%202015_UK.pdf
- [2] Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014: estimates of diabetes and its burden in the United States [Internet]. Atlanta, GA: U.S. Department of Health and Human Services; 2014. Available from:
<http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>.
- [3] Linnebjerg H, Lam EC, Seger ME, Coutant D, Chua L, Chong CL, et al. Comparison of the Pharmacokinetics and Pharmacodynamics of LY2963016 Insulin Glargine and EU- and US-Approved Versions of Lantus Insulin Glargine in Healthy Subjects: Three Randomized Euglycemic Clamp Studies. *Diabetes Care*. 2015 Dec;38(12):2226-33.
- [4] Heise T, Hovelmann U, Nosek L, Hermanski L, Bottcher SG, Haahr H. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert Opin Drug Metab Toxicol*. 2015 Aug;11(8):1193-201.
- [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 Jun;240(6):E630-9.
- [6] Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man. A novel mechanism for insulin resistance. *J Clin Invest*. 1990 Jun;85(6):1844-52.
- [7] Argoud GM, Schade DS, Eaton RP. Underestimation of hepatic glucose production by radioactive and stable tracers. *Am J Physiol*. 1987 May;252(5 Pt 1):E606-15.
- [8] Henry RR, Mudaliar S, Ciaraldi TP, Armstrong DA, Burke P, Pettus J, et al. Basal insulin peglispro demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy subjects. *Diabetes Care*. 2014 Sep;37(9):2609-15.

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:

- o The biology of how drugs/vaccines work
- o Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- o Other pathways drugs/vaccines may interact with
- o 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 (clinical.specimen.management@merck.com).

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 clinical.specimen.management@merck.com.

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/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html>
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

| Part 1 – MK-1092/Glargine Subcutaneous in Healthy Subjects | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|-----------|------------------|------------|-------------------|-------------------|----------------|
| Laboratory safety tests + FSH (if applicable) ^a | 1 | | | 1 | 7 | 7 |
| Laboratory safety tests | 1 | 3 | 1 | 5 | 5.5 | 27.5 |
| HIV/Hepatitis Screen | 1 | | | 1 | 10 | 10 |
| Serum NEFA and C-peptide | | 3 | | 3 | 5 | 15 |
| Blood for glycerol | 1 | 6 | | 7 | 2 | 14 |
| Serum NEFA, C-peptide and Ketones | | 3 | | 3 | 8.5 | 25.5 |
| Serum Insulin, NEFA, C-peptide & Ketones ^b | 1 | | | 1 | 8.5 | 8.5 |
| Blood for Immunogenicity Assay | 1 | | 2 | 3 | 6 | 18 |
| Blood for Planned Genetic Analysis | 1 | | | 1 | 8.5 | 8.5 |
| Blood for MK-1092/Glargine PK Assay | 1 | 18 | 2 | 21 | 6 | 126 |
| Blood for YSI Plasma Glucose | 1 | 76 | | 77 | 0.5 | 38.5 |
| Total Blood Volume Per Subject ^c | | | | | | 298.5mL |
| ^a Laboratory safety tests conducted at screening. FSH to be conducted only for postmenopausal females without menses for at least 1 year. ^b Pre-dose sample ^c If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. | | | | | | |

| Part 2 – MK-1092 Subcutaneous in Healthy Subjects + Humalog IV | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|------------------|-------------------------|-------------------|------------------------------|------------------------------|---------------------------|
| Laboratory safety tests + FSH (if applicable) ^a | 1 | | | 1 | 7 | 7 |
| Laboratory safety tests | 1 | 3 | 1 | 5 | 5.5 | 27.5 |
| HIV/Hepatitis Screen | 1 | | | 1 | 10 | 10 |
| Serum NEFA and C-peptide | | 3 | | 3 | 5 | 15 |
| Blood for glycerol | 1 | 6 | | 7 | 2 | 14 |
| Serum NEFA, C-peptide and Ketones | | 3 | | 3 | 8.5 | 25.5 |
| Serum Insulin, NEFA, C-peptide & Ketones ^b | 1 | | | 1 | 8.5 | 8.5 |
| Blood for Immunogenicity Assay | 1 | | 2 | 3 | 6 | 18 |
| Blood for Planned Genetic Analysis | 1 | | | 1 | 8.5 | 8.5 |
| Blood for MK-1092 PK Assay | 1 | 19 | 2 | 22 | 6 | 132 |
| Blood for Humalog PK Assay | 1 | 8 | | 9 | 5 | 45 |
| Blood for YSI Plasma Glucose | 1 | 76 | | 77 | 0.5 | 38.5 |
| Total Blood Volume Per Subject ^c | | | | | | 349.5mL |
| ^a Laboratory safety tests conducted at screening. FSH to be conducted only for postmenopausal females without menses for at least 1 year. ^b Pre-dose sample ^c If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. | | | | | | |

| Part 3 – MK-1092/Glargine Subcutaneous in Subjects with T1DM | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|--|------------------|-------------------------|-------------------|------------------------------|------------------------------|---------------------------|
| Laboratory safety tests + FSH (if applicable) ^a | 1 | | | 1 | 7 | 7 |
| Laboratory safety tests | 1 | 3 | 1 | 5 | 5.5 | 27.5 |
| HIV/Hepatitis Screen | 1 | | | 1 | 10 | 10 |
| Serum NEFA only | | 3 | | 3 | 3.5 | 10.5 |
| Blood for glycerol | 1 | 6 | | 7 | 2 | 14 |
| Serum NEFA and Ketones | 1 | 3 | | 4 | 5 | 20 |
| Serum C-peptide only ^b | 1 | | | 1 | 3.5 | 3.5 |
| Blood for HbA1c | 1 | | | 1 | 2 | 2 |
| Blood for Immunogenicity Assay | 1 | | 2 | 3 | 6 | 18 |
| Blood for Planned Genetic Analysis | 1 | | | 1 | 8.5 | 8.5 |
| Blood for MK-1092/Glargine PK Assay | 1 | 18 | 2 | 21 | 6 | 126 |
| Blood for YSI Plasma Glucose ^c | 1 | 24 | | 25 | 0.25 | 6.25 |
| Total Blood Volume Per Subject ^d | | | | | | 253.25mL |
| ^a Laboratory safety tests conducted at screening. FSH to be conducted only for postmenopausal females without menses for at least 1 year. ^b C-peptide conducted at screening ^c YSI volume and sampling frequency per site's revised SOP. ^d If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. | | | | | | |

| Part 4 – MK-1092/Glargine Subcutaneous in Subjects with T2DM | Pre-trial | Treatment Period | Post-trial | Total Collections | mL Per Collection | Total mL/ Test |
|---|------------------|-------------------------|-------------------|--------------------------|--------------------------|-----------------------|
| Laboratory safety tests + FSH (if applicable) ^a | 1 | | | 1 | 7 | 7 |
| Laboratory safety tests | 3 | 9 | 1 | 13 | 5.5 | 71.5 |
| HIV/Hepatitis Screen | 1 | | | 1 | 10 | 10 |
| Blood for glycerol | 3 | 11 | | 14 | 2 | 28 |
| Serum NEFA, C-peptide and Ketones | 3 | 7 | | 10 | 8.5 | 85 |
| Serum NEFA and C-peptide | | 4 | | 4 | 5 | 20 |
| Blood for HbA1c | 1 | | | 1 | 2 | 2 |
| Blood for Immunogenicity Assay | 1 | | 2 | 3 | 6 | 18 |
| Blood for Planned Genetic Analysis | 1 | | | 1 | 8.5 | 8.5 |
| Blood for MK-1092/Glargine PK Assay | 3 | 36 | 2 | 41 | 6 | 246 |
| Blood for YSI Plasma Glucose ^b | | 72 | | 72 | 0.25 | 18 |
| Total Blood Volume Per Subject ^c | | | | | | 514mL |
| ^a Laboratory safety tests conducted at screening. FSH to be conducted only for postmenopausal females without menses for at least 1 year. ^b YSI volume and sampling frequency per site's revised SOP. ^c If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, including additional YSI blood glucose measurements during the clamp procedure for safety, additional blood (up to 100 mL) may be obtained. | | | | | | |

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 \geq 25 bpm from baseline |
| Sinus Bradycardia | < 40 bpm | HR < 40 bpm and HR decrease of \geq 5 bpm from baseline |
| Sinus Pause/Arrest | > 2.0 seconds | > 2.0 seconds |
| Atrial premature complex | > 1 beat | \geq 3 beats |
| Ventricular premature complex | All | \geq 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 \geq 230 ms | PR \geq 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 \geq 130 ms | QRS \geq 130 ms + increase of \geq 10 ms |
| QTc (B or F) | | |
| Male | QTc \geq 450 ms | QTc \geq 500 ms or increase of \geq 60 ms from baseline |
| Female | QTc \geq 450 ms | QTc \geq 500 ms or increase of \geq 60 ms from baseline |

| 12-Lead Electrocardiogram Abnormality Criteria | | |
|---|---|--|
| | Screen Failure Criteria^a | Potentially Significant Post-Randomization Findings (clarification on action to take)^b |
| HYPERTROPHY | | |
| Atrial abnormalities | Definite evidence of P mitrale or P pulmonale | Definite evidence of P mitrale or P pulmonale |
| 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 to determine whether the individual may be included in the study. ^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 \geq 500 ms

If the QTc interval is \geq 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 \geq 60 ms

During each treatment period, if a subject demonstrates an increase in QTc interval \geq 60 msec compared with median predose baseline measurement, the ECG will be repeated twice within 5 minutes. The median value of the QTc interval from the 3 ECGs will represent the value at that time point. If the QTc interval increase from baseline for any postdose time point is \geq 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 \geq 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 mg/dL with symptoms and glucose values ≤ 50 mg/dL with or without symptoms. Fingerstick measurements (as opposed to CGM) should be used when possible to assess a potential hypoglycemia AE.

- If there are symptoms associated with low glucose (≤ 70 mg/dL), this is a **clinical** AE with a diagnosis of hypoglycemia.
- If there are no symptoms associated with a low glucose (> 50 mg/dL ≤ 70 mg/dL) 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 mg/dL 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 measurements (as opposed to CGM) should be used when possible to assess a potential hyperglycemia AE.

- 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 via insulin pump or injection, initiation or increase in the rate of a SC infusion of short-acting insulin via insulin pump, and initiation or increase in the rate of an IV infusion of insulin. The dose and/or frequency of MK-1092/comparator insulin (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 | |