Official Protocol Title:	A Phase IIa, Multicenter, Placebo- and Active-controlled, Randomized, Double-Blind, Clinical Trial to Evaluate the Safety and Efficacy of MK-8521 Compared to Placebo in Subjects with Type 2 Diabetes Mellitus
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TITLE:

A Phase IIa, Multicenter, Placebo- and Active-controlled, Randomized, Double-Blind, Clinical Trial to Evaluate the Safety and Efficacy of MK-8521 Compared to Placebo in Subjects with Type 2 Diabetes Mellitus

IND NUMBER: 119,329
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1	Trial Design	Added details regarding the planned interim analysis.	Provided clarity and details regarding the aspects of interim analyses to be performed. • Re-evaluation of sample size • Guidelines for potential termination of the study • Differentiation of the safety triggered review from the planned interim analyses
4.2.3.1	Efficacy Endpoints	Removed text regarding the interim analysis.	
5.12	Clinical Criteria for Early Trial Termination	Updated text to reflect changes based on the planned interim analysis.	
7.3.2	Data Monitoring Committee	Added details regarding the planned interim analysis.	
8.1.4	Interim Analysis	Added a planned interim analysis to potentially increase the sample size or terminate the study for futility.	
8.2.1	Responsibility for Analyses/In-House Blinding	Added additional detail regarding approach to unblinding for the planned interim analysis	
8.2.9.1	Safety Review for Discontinuation Due to HR	Section title was changed to *Triggered Safety Review for Discontinuation Due to HR*.	
8.2.9.2	Efficacy and Safety Review for Planning Future Studies	Section title was changed to *Planned Efficacy and Safety Review*. Text was modified to explain the planned interim analyses and possible actions including study termination or increase sample size.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.2	Trial Diagram	Trial diagram was corrected to indicate A1C requirement of 7.5-10.5% at V2.	Corrected typographical error. Trial diagram incorrectly indicated A1C requirement of 7.5-10.5% at V3.
5.5	Concomitant Medication (Allowed & Prohibited)	Removed text stating that subjects continue to take their own supply of metformin as prescribed by their primary care physician while they are in the trial.	Prescriptions for metformin may be written by primary care physician or study investigator.
5.1.3 5.5	Subject Exclusion Criteria Concomitant Medications/Vaccinations (Allowed and Prohibited)	• Added Note indicating that systemic and ophthalmic beta blockers are prohibited. • Added additional examples of beta blocker or medications with sympathomimetic activity.	Provides clarity on exclusion criterion and prohibited medication use.
6.0	Trial Flow Chart	• Updated footnote b to include body weight, chemistry and hematology as required procedures at the 14-Day Post Treatment Follow-Up Visit. • Added footnote bb to indicate when to obtain and send to central laboratory PK samples for MK8521 or Liraglutide	• Corrected inconsistencies between protocol sections. • Clarified that if a subject is randomized to Liraglutide (open label), only the PK samples for Liraglutide should be obtained and sent to the central laboratory (and PK samples for MK-8521 should not be obtained). Conversely, if a subject is randomized to MK-8521/placebo only PK samples for MK-8521 should be obtained and sent to the central laboratory (and PK samples for Liraglutide should not be obtained).

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.1	Vitals Signs (Sitting Blood Pressure and Heart Rate)	Removed text referring to recording last set of BP and HR measurements in source.	All BP and HR measurements should be recorded in source.
7.1.3.2	Pharmacokinetic/Pharmacodynamic Evaluations	Added text indicating when to obtain and send to central laboratory PK samples for MK8521 or Liraglutide	Clarified that if a subject is randomized to Liraglutide (open label), only the PK samples for Liraglutide should be obtained and sent to the central laboratory (and PK samples for MK-8521 should not be obtained). Conversely, if a subject is randomized to MK-8521/placebo only PK samples for MK-8521 should be obtained and sent to the central laboratory (and PK samples for Liraglutide should not be obtained).
8.2.4.1	Efficacy Analysis Population	• Expanded PP drug compliance violation to exclude subjects who have high likelihood of poor compliance based on PK data and to exclude all subjects from sites with a high degree of non-compliance based on PK data. • Clarified that the PP exclusion regarding inability to tolerate MK-8521 applies only to the 300 µg group • Added modified FAS population.	• Utilize PK data to assess compliance • Clarification • Permit assessment of efficacy excluding data from sites with high degree of non-compliance as assessed by PK

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.2.4.2	Safety analysis populations	• Added modified ASaT population.	• To permit safety analysis excluding data from sites with high degree of non-compliance as assessed by PK
8.2.5.1	Efficacy Analyses	• Change and percent change from baseline in triglycerides will be analyzed using a robust regression approach. • The primary (A1C) and key secondary endpoints (FPG and body weight) will also be analyzed using an ANCOVA model in the PP population. • Added modified FAS population for analysis	• Because change and percent change in triglycerides typically has a skewed distribution, the cLDA model which is based on the symmetric normal distribution may not be appropriate. • ANCOVA model is more appropriate than cLDA for PP population. • Rationale provided above (Section 8.2.4.1)
8.2.5.2	Safety Analyses	• Added modified ASaT population	• Rationale provided above (Section 8.2.4.2)
8.2.6	Multiplicity	Modified text related to type 1 error control related to the interim analysis described in Section 8.1.4.	• Clarification

1.0 TRIAL SUMMARY

Abbreviated Title	MK-8521 Phase IIa Trial in Subjects with Type 2 Diabetes Mellitus
Trial Phase	IIa
Clinical Indication	Treatment of type 2 diabetes mellitus in patients with inadequate glycemic control with metformin monotherapy
Trial Type	Interventional
Type of control	Placebo and Active
Route of administration	Subcutaneous
Trial Blinding	Double-blind
Treatment Groups	MK-8521 300 µg (dose to be gradually escalated over the first 3 weeks up to 300 µg), or MK-8521 180 µg (dose to be gradually escalated over the first 2 weeks up to 180 µg), or Placebo to MK-8521 (mock escalation over the first 2-3 weeks), or open-label liraglutide (dose to be gradually escalated over the first 2 weeks up to 1.8 mg) for 12 weeks.
Number of trial subjects	Approximately 160 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 20 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to approximately 25 weeks from the time the subject signs the Informed Consent Form (ICF) through the final contact. This will include a 1-week screening period (Visit 1 to Visit 1A or Visit 2); an 8-week antihyperglycemic agent (AHA) washout period (Visit 1A to Visit 2) if required; a 2-week single-blind placebo run-in period (Visit 2 to Visit 3); a 12-week treatment period (Visit 3 to Visit 10) and a post-treatment visit 2 weeks after the last dose of investigational product.
Randomization Ratio	1:1:1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter randomized, double-blind, placebo- and active-controlled (liraglutide; Victoza®), parallel-group, clinical trial of MK-8521 in subjects with T2DM on a stable dose of metformin (≥1000 mg/day). This trial will be conducted in conformance with Good Clinical Practices (GCP).

The duration of the trial will be up to 25 weeks (with up to 12 clinic visits) for each subject. This will include a 1-week screening period (Visit 1 to Visit 1A or Visit 2); if required, an antihyperglycemic agent (AHA) washout period of at least 8 weeks (Visit 1A to Visit 2); a 2-week single-blind placebo run-in period (Visit 2 to Visit 3); a 12-week placebo- and active-controlled treatment period (Visit 3 to Visit 10); and a 14-day post-treatment visit 2 weeks after the last dose of investigational product.

Approximately 160 subjects ≥21 and ≤65 years of age with T2DM, diagnosed in accordance with American Diabetes Association guidelines with inadequate glycemic control (hemoglobin A1c [A1C] ≥7.5% and ≤10.5% [≥58 mmol/mol and ≤91 mmol/mol]) while on a stable dose of metformin monotherapy ≥1000 mg/day and who meet all enrollment criteria

will be randomized. Subjects will continue on their stable dose of metformin throughout the trial including the 14-day post-treatment visit.

Management of Subjects Prior to Randomization

Pre-randomization management of subjects is summarized in Table 1 below. At Visit 1/Screening, subjects who meet criteria for one of the two groups presented in Table 1, based on their anti-hyperglycemic agent (AHA) status and A1C, and also meet other study eligibility criteria detailed in Section 5.0, will be eligible for enrollment.

Management between Visit 1/screening and Visit 2/initiation of placebo run-in will differ depending on AHA status at screening as follows:

- Subjects on metformin monotherapy at screening will proceed to Visit 2/Week -2, at which time they will receive diet and exercise counseling and enter a 2 week placebo run-in period. If they continue to meet eligibility criteria, randomization will occur at Visit 3/Day 1.
- Subjects on dual AHA therapy (metformin plus a second permissible AHA) will proceed to Visit 1A, at which time they will receive diet and exercise counseling and initiate washout of the non-metformin agent. The washout period will be at least 8 weeks, after which they will proceed to Visit 2/Week -2 and enter a 2 week placebo run-in period. If they continue to meet eligibility criteria, randomization will occur at Visit 3/Day 1.

Eligibility for continued study participation will be assessed at Visits 1, 2, and 3 (Randomization/Day 1) based on the criteria detailed in Section 5.1. For subjects for whom Visit 2 occurs more than 2 weeks after Visit 1 (including all subjects undergoing washout), this includes the requirement, that A1C at Visit 2 be ≥7.5% and ≤10.5% (≥58 mmol/mol and ≤91 mmol/mol) and that required laboratory results (see Flow Chart, Section 6.0) are consistent with enrollment criteria.

Note: If Visit 2 occurs ≤ 2 weeks after Visit 1, then repeat A1C and screening laboratories should **not** be conducted.

The placebo run-in may be initiated at Visit 2/Week -2 while laboratory data, including A1C, are pending, but randomization may not occur until all eligibility criteria are confirmed. If a subject has initiated the placebo run-in but screen fails due to A1C or other laboratory data collected at Visit 2, they should be contacted and told to discontinue the placebo run-in.

For subjects who meet enrollment criteria at Visit 1 except for elevated triglycerides (TG) and/or elevated blood pressure, the investigator may initiate or adjust lipid-lowering and/or blood pressure medication and permit the subject to proceed with pre-randomization activities. **Note the following for these subjects:**

- All modification of lipid-lowering and/or blood pressure medication must occur prior to Visit 2/Week -2 (with unscheduled visits, as needed).
- Lipid-lowering and/or blood pressure medications must be at a stable dose for at least 4 weeks prior to Visit 3/randomization. The screening period (Visit 1 to Visit 2) should be extended as necessary to meet this requirement.

• Subjects for whom lipid-lowering medication is initiated or modified to address elevated TG must meet TG eligibility criteria at Visit 2 to proceed to randomization. All subjects must meet blood pressure eligibility criteria at Visit 3/randomization to proceed with randomization.

Placebo Run-In

At **Visit 2/Week -2**, eligible subjects will enter the 2-week, single-blind, placebo run-in period. All subjects (including those subjects who will eventually be randomized to open-label liraglutide) will be dispensed 2 vials/day single-blind investigational product (referred to as **Vial A** and **Vial B** (MK-8521 180 µg and MK-8521 300 µg matching placebos, respectively) and instructed to take one injection (0.1 mL) per day **from each vial** at approximately the same time of day in the morning during the 2-week single-blind placebo period prior to randomization. Subjects should be reminded to withhold single-blind investigational product on the day of **Visit 3/ Day 1**. **Note:** Subjects who miss more than one daily dose (i.e., 2 injections on the same day or 2 single injections on separate days) of the placebo run-in medication are ineligible for randomization.

Subjects meeting eligibility for randomization through Visit 3/Day 1, based on the criteria detailed in Section 5.1, will be eligible to enter the double-blind treatment period.

Table 1 Pre-Randomization Management

Regimen at Visit 1/ Screening	Visit 1/Screening A1C Entry Criterion	Subject Management during the Pre-Randomization Period
On metformin monotherapy (≥1000 mg/day) for ≥12 weeks	A1C ≥7.5% and ≤10.5% (≥58 mmol/mol and ≤91 mmol/mol)	• Continue metformin at Visit 1 dose throughout the trial. • Proceed to Visit 2/Week -2 and initiate placebo run-in as appropriate • Randomize at Visit 3 if subject continues to be eligible.
On dual therapy of metformin (≥1000 mg/day for ≥4 weeks) and a second AHA[1]	A1C ≥7.0% and ≤10.0% (≥53 mmol/mol and ≤86 mmol/mol)	• Continue metformin at Visit 1 dose throughout the trial. • Discontinue treatment with other AHA at Visit 1A/Washout • Proceed to Visit 2/Week -2 after an AHA washout of ≥8 weeks. Initiate placebo run-in as appropriate • Randomize at Visit 3 if subject continues to be eligible[2]
[1]Allowable AHAs prior to screening (Visit 1): DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides. [2]Randomization requirements include Visit 2 A1C ≥7.5% and ≤10.5% (≥58 mmol/mol and ≤91 mmol/mol)		

Management of Randomized Subjects

At **Visit 3/Day 1**, subjects who meet enrollment criteria will enter the 12-week treatment period. Subjects will be randomized in a 1:1:1:1 ratio to 1 of 4 treatment groups: (1) MK-8521 300 µg once-daily (QD), (2) MK-8521 180 µg QD, (3) MK-8521 placebo QD, (4) open-label liraglutide 1.8 mg QD. All treatments will be administered with subcutaneous injection. Subjects are to remain on their stable dose of metformin (≥1000 mg/day) while receiving investigational product (blinded or open-label) during the treatment period.

Subjects randomized to either MK-8521 180 µg or 300 µg or placebo will have a 2 and 3 step dose escalation regimen, respectively, to achieve the planned study dose (see Table 6, Section 5.2.1.2). Subjects randomized to liraglutide will have a 2 step dose escalation regimen to achieve the planned study dose.

A double-dummy approach will be used in the trial because the volume of MK-8521 administered differs between the 180 µg and 300 µg dose arms. With the double-dummy approach, subjects randomized to MK-8521 or MK-8521 placebo will administer 2 injections each day: 1 injection from **Vial C** containing active MK-8521 180 µg dose or placebo and 1 injection from **Vial D** containing MK-8521 300 µg or placebo. Subjects randomized to the MK-8521 180 µg group will also receive placebo for MK-8521 300 µg; subjects randomized to the MK-8521 300 µg group will also receive placebo for MK-8521 180 µg; subjects randomized to placebo will receive placebo for both MK-8521 300 µg and MK-8521 180 µg. Subjects randomized to liraglutide will receive only open-label liraglutide for the duration of the trial.

MK-8521 or MK-8521 Placebo Dosing

For subjects randomized to the MK-8521 300 µg treatment group, Vial C will contain placebo and Vial D will contain active MK-8521. The starting dose in the MK-8521 300 µg treatment group will be 60 µg (0.1 mL from each vial) from Visit 3/Day 1 through Day 6. The dose will then be escalated to 120 µg (0.2 mL from each vial) from Visit 4/Week 1 through Day 13, to 180 µg (0.3 mL from each vial) from Visit 5/Week 2 through Day 20, and to the final dose of 300 µg (0.3 mL from Vial C and 0.5 mL from Vial D) from Visit 6/Week 3 for the remainder of the 12 weeks (approximately 63 days).

For subjects randomized to the MK-8521 180 µg treatment group, Vial C will contain active MK-8521 and Vial D will contain placebo. The starting dose in the MK-8521 180 µg treatment group will be 60 µg (0.1 mL from each vial) from Visit 3/Day 1 through Day 6. The dose will then be escalated to 120 µg (0.2 mL from each vial) from Visit 4/Week 1 through Day 13, and to the final dose of 180 µg (0.3 mL from each vial) from Visit 5/Week 2 through Day 20. In order to maintain blinding with the MK-8521 300 µg treatment group (see above), the dose from Vial C will remain at 0.3 mL/day and the dose Vial D will increase to 0.5 mL/day from Visit 6/Week 3 for the remainder of the 12 weeks (approximately 63 days).

In order to maintain blinding with the MK-8521 treatment arms, subjects randomized to placebo will receive a dose escalation regimen consistent with that for MK-8521 300 µg and 180 µg treatment groups (see above). For subjects randomized to the Placebo treatment group, both Vial C and Vial D will contain placebo. The starting dose in the Placebo treatment group will be 0.1 mL from each vial from Visit 3/Day 1 through Day 6. The dose will then be escalated to 0.2 mL from each vial from Visit 4/Week 1 through Day 13, to 0.3 mL from each vial from Visit 5/Week 2 through Day 20, and to the final dose of 0.3 mL from Vial C and 0.5 mL from Vial D from Visit 6/Week 3 for the remainder of the 12 weeks (approximately 63 days).

Subjects who cannot tolerate 0.5 mL/day from Vial D may continue in the trial on 0.3 mL/day (180 µg/day for subjects randomized to active MK-8521) from each vial (refer to Section 5.2.1.2 for further details).

Liraglutide Dosing

Subjects randomized to the liraglutide 1.8 mg treatment group will start at a dose of liraglutide 0.6 mg from Visit 3/Day 1 through Day 6, 1.2 mg from Visit 4/Week 1 through Day 13 and 1.8 mg from Visit 5/Week 2 for the remainder of the 12 weeks (approximately 70 days).

Subjects who cannot tolerate the 1.8 mg/day dose of liraglutide may continue in the trial on the 1.2 mg/day dose.

Subjects who are discontinued from investigational product (blinded or open-label) for any reason other than withdrawal of consent will be followed by telephone contacts for the duration of the trial according to the Trial Flow Chart - Section 6.0. The purpose of the telephone contacts will be to assess for SAEs. All subjects will perform a post-treatment visit 14 days after the last dose of investigational product. The purpose of the 14-day post treatment visit will be to assess for safety/efficacy parameters.

Interim analysis

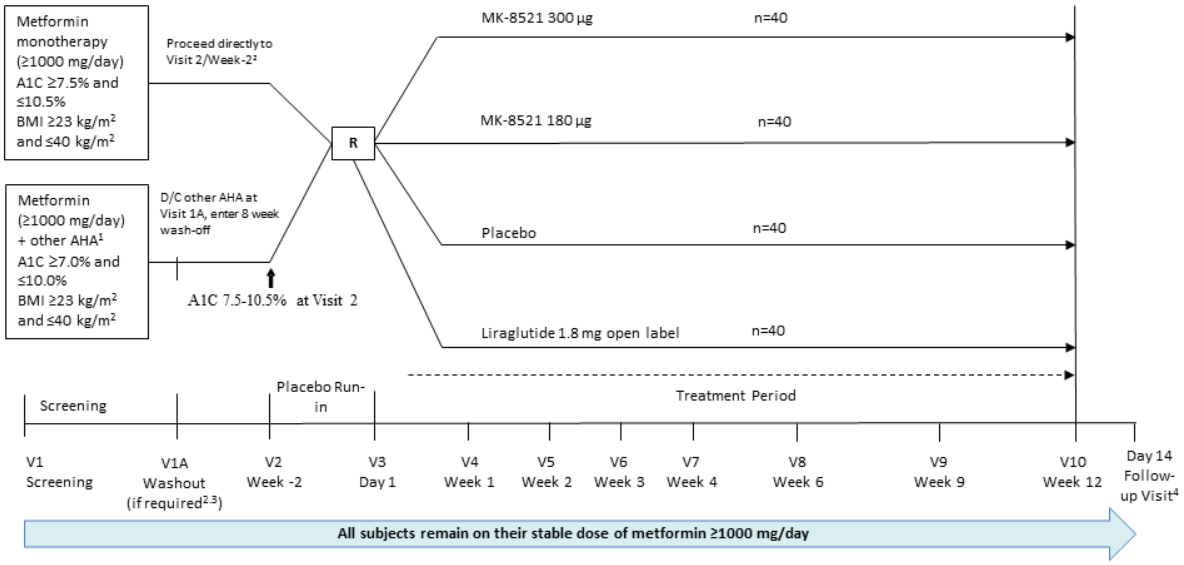
An interim analysis will be performed when at least 50% of subjects have completed the Week 12 Visit or discontinued prior to the Week 12 Visit and will include an assessment of both efficacy endpoints (including A1C and weight loss) and safety endpoints (including AEs and change from baseline in heart rate). One of the goals of this interim analysis will be to determine whether the study has sufficient potential to demonstrate the necessary efficacy and safety profile to justify continued development of MK-8521. If so, the study will continue to completion. If not, the study will be terminated. An additional goal of the interim analysis is sample size re-estimation. The results of this interim analysis will be reviewed by the Sponsor standing internal Data Monitoring Committee (siDMC). The approach to the interim analysis is described in more detail in Section 8.2.9.

This trial is designed to evaluate the safety and tolerability of the addition of treatment with MK-8521 to the regimen of adult subjects with T2DM and inadequate glycemic control on diet, exercise and metformin monotherapy. It is also designed to evaluate the effect of MK-8521 on glycemic control and body weight following a 12-week dosing period as compared to placebo and with reference to liraglutide.

Please note, throughout this protocol, “Sponsor” refers to “Sponsor or its delegate” and “Subsidiary” refers to “Subsidiary or designee”.
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.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



[1]Allowable AHAs at Screening (Visit 1) are: DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides.
[2]If lipid-lowering or blood pressure medication requires initiation or adjustment, adjustments should be made prior to Visit 2/Week -2 (with unscheduled visits, as needed). The screening period (Visit 1 to Visit 2) should be extended so that subjects are on a stable regimen for at least 4 weeks prior to Visit 3/Day 1. Subjects requiring AHA washout can have adjustments made concurrently with AHA washout.
[3]Visit 1A/Washout is required if a subject requires AHA washout. If necessary, adjustment or initiation of lipid-lowering or blood pressure medication can also be performed at the visit.
[4]Subjects who complete Visit 10 or those who discontinue early will have the Follow-up Visit 14 days after the last dose of investigational product.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with T2DM with inadequate glycemic control on metformin monotherapy, after 12 weeks of once-daily administration:

1. **Objective:** To assess the A1C-lowering efficacy of the addition of MK-8521 relative to placebo.

   Hypothesis: 300µg/day or both doses of MK-8521 provide greater reduction in A1C relative to placebo.

2. **Objective:** To evaluate safety and tolerability of MK-8521.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with T2DM with inadequate glycemic control on metformin monotherapy, after 12 weeks of once-daily administration of MK-8521, to assess the effect relative to placebo on:

1. Body weight

   Hypothesis: 300µg/day or both doses of MK-8521 reduce body weight relative to placebo.

2. Fasting plasma glucose

   Hypothesis: 300µg/day or both doses of MK-8521 provide greater reduction in FPG relative to placebo.

3. Fasting lipids (including LDL-cholesterol level, HDL-cholesterol level, triglyceride level).

4. Systolic and diastolic blood pressure

   In subjects with T2DM with inadequate glycemic control on metformin monotherapy, after 12 weeks of once-daily administration of MK-8521, to estimate the effect relative to liraglutide on:

5. Glycemic measures (A1C and FPG)

6. Body weight

7. Fasting lipids (including LDL-cholesterol level, HDL-cholesterol level, triglyceride level).

8. Systolic and diastolic blood pressure

3.3 Exploratory Objectives

1. **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will 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-8521.

4.1.1 Pharmaceutical and Therapeutic Background

There has been an increase in the global prevalence of T2DM largely attributed to rising rates of excess body weight and obesity. Approximately 85% of patients with T2DM are obese or overweight, a key factor underlying the development and maintenance of insulin resistance and pancreatic β cell failure [1, 2]. Pharmacological agents that lower glucose while also lowering body weight represent a major advantage in the treatment of diabetes.

Among new therapies for T2DM, peptidyl mimetics of the gut-derived incretin hormone glucagon-like peptide 1 (GLP-1) stimulate insulin biosynthesis and secretion in a glucose-dependent manner and cause modest weight loss. Several of these agents are currently approved for the treatment of patients with T2DM (including exenatide [Byetta™ and Bydureon™]) and liraglutide [Victoza™]) [3].

Glucagon acutely increases hepatic glucose production and subsequently raises blood glucose levels. However, emerging evidence suggests that glucagon receptor (GCGR) activation may also mediate a post prandial satiety signal [4] and with chronic stimulation may result in weight loss [5]. In preclinical murine models, combined tonic activation of both the GLP-1 receptor (GLP-1R) and the GCGR resulted in anti-hyperglycemic activity with significant weight loss (superior to incretin action) [6]. Likewise, in healthy overweight/obese volunteers, co-administration of GLP-1 during glucagon infusion resulted in increased energy expenditure without hyperglycemia (of note, administration of glucagon alone caused a rise in blood glucose and GLP-1 alone did not cause any change in energy expenditure) [7].

Oxyntomodulin (OXM), an endogenous gut-derived peptide agonist of both the GLP-1R and the GCGR, has been suggested to reduce food intake and body weight, increase energy expenditure, improve glucose metabolism and promote weight loss in both rodents and overweight and obese humans [8-9]. In a study by Wynne *et.al*, 26 participants with a BMI of 25 - 40 kg/m^2 self-administered saline or OXM subcutaneously for 4 weeks in a randomized, double-blind, parallel-group protocol. Body weight was reduced by 2.3 ± 0.4 kg in the treatment group over the study period compared with 0.5 ±0.5 kg in the control group (P =0.011) [8]. Energy intake by the active treatment group was significantly reduced by 170 ± 37 kcal (25 ± 5%) at the initial study meal (P >0.001) and by 250 ± 63 kcal (35 ± 9%) at the final study meal (P = 0.002). In a subsequent study by Wynne *et.al*, fifteen healthy overweight and obese men and women (age: 23–49 years, BMI: 25.1–39.0 kg/m^2) self-administered subcutaneous OXM or placebo, three times daily for four days. Energy expenditure was measured by indirect calorimetry and combined heart rate (HR) and movement monitoring. OXM did not alter resting energy expenditure but increased activity-related energy expenditure by 143±109 kcal/day or 26.2±9.9% (P=0.022), total energy expenditure by 9.4±4.8% (P=0.045) and physical activity level by 9.5±4.6% (P=0.049). A reduction in body weight of 0.5±0.2% was observed during the OXM administration period (P=0.023) [9].

MK-8521 is an acylated peptide that has agonist effects at both GLP-1R and GCGR, and hence can be considered a dual receptor agonist. By augmenting both weight loss and exerting a glucose-lowering effect, dual agonism may provide a more effective strategy than GLP-1 only targeted peptides. The program hypothesis is that the activation of these two receptors by MK-8521 should lead to an additive effect on body weight loss (greater than that observed with GLP-1R agonists) and a glucose lowering effect similar to that observed with GLP-1R agonists. Dual activation of the GLP-1R and the GCGR is anticipated to lead to glucose lowering via several mechanisms:

- A rapid acting mechanism via augmentation of insulin secretion and inhibition of gastric emptying by GLP-1R agonism (possibly further stimulated by GCGR agonism [10,11]).
- A slower mechanism via complementary induction of body weight loss by GLP-1R and GCGR agonism.

This is the fourth clinical study with MK-8521, and the second in which MK-8521 will be administered to subjects with T2DM.

The objective of this trial is to evaluate the safety/tolerability and efficacy (focusing on change in A1C and body weight vs. placebo, using liraglutide as a reference) of MK-8521 administered to a cohort of T2DM subjects on a stable dose of metformin in an outpatient setting for 12 weeks. Two doses of MK-8521 will be evaluated and will provide a better understanding of the correlation between dose and safety and efficacy parameters (including weight loss and glycemic control). Liraglutide is included to provide a reference arm for both efficacy and safety endpoints.

4.1.2 Completed Pre-clinical and Clinical Trials

4.1.2.1 Completed Pre-clinical Trials

In pre-clinical trials, MK-8521 has demonstrated robust glucose-lowering and weight loss properties in diabetic rhesus monkeys and was evaluated in 12-week toxicology studies in rats and rhesus monkeys to support further clinical testing. Pharmacology and toxicology data are reviewed in detail in the IB.

4.1.2.2 Completed Clinical Trials

As of November 2014, MK-8521 has been evaluated in three clinical trials (P001, P002 & P003). See the IB and Table 2 for MK-8521 clinical program overview.

Table 2 MK-8521 Clinical Program Overview

Activity	Protocol	Pop	N	MK-8521 Dose Range (µg/day)	Comparator	Dosing Duration (Days)	Setting
Single Dose							
Single rising dose	P001 (eCTA) and P002	Lean healthy volunteers	32	Up to 300 µg/day	Placebo	Single dose	Domiciled
Graded glucose infusion	P001 and P002	Lean healthy volunteers	22	35 µg/day -125 µg/day	Placebo	Single dose	Domiciled
Multiple Dose							
Multiple rising dose	P002	Lean healthy volunteers, Obese healthy volunteers (1 panel)	MK-8521 :6/ panel placebo: 2/ panel	Up to 150 µg/day	Placebo	10-14	Domiciled
Ph1B inT2DM	P003 Part I	Obese T2DM on metformin	MK-8521: 8 Liraglutide:8 Placebo: 8	Up to 120 µg/day	Placebo, liraglutide 1.8 mg	14	Domiciled
	P003 Part II	Obese T2DM on metformin	MK-8521: 18 Liraglutide: 12 Placebo: 6	Titration 64 µg/day – 300 µg/day over 29 days	Placebo Liraglutide titrated to 1.8 mg/day	29	Domiciled

A total of approximately 86 healthy male subjects have enrolled and approximately 70 healthy male subjects have been exposed to subcutaneous MK-8521 as a single dose ranging from 2- 300 µg and multiple daily doses for up to 14 days ranging from 50 to 150 µg/day. A total of approximately 79 male and female T2DM and 16 male and female non-diabetic obese /overweight subjects have been enrolled and approximately 48 of these subjects have been exposed to subcutaneous MK-8521 as multiple doses for up to 29 days at doses ranging from 34-300 µg. MK-8521 has been generally well tolerated up to 29 days of dosing, and robustly lowered glucose in subjects with T2DM (P003). Potential safety issues that have manifested in clinical testing to date include GI intolerance and HR increases. Both appear to be generally consistent with effects reported for other agents in the GLP-1R agonist class.

Clinical Pharmacokinetics (PK)

MK-8521 PK properties have been generally consistent across the tested dose range, over time, and between populations with the exception of the apparent impact of BMI as noted below. MK-8521 is slowly absorbed post single subcutaneous administration at doses ranging from 2 – 300 µg, with a median T_{max} of ~ 10-14 hr, and eliminated after T_{max} in a mono-exponential manner, with an apparent terminal half-life ($t_{1/2}$) of ~13-15 hr. Preliminary multiple dose PK data show that steady state (SS) appears to be achieved within 4-5 days of MK-8521 following multiple daily administrations in subjects with T2DM with accumulation

ratios of approximately 2 fold. Plasma exposures of MK-8521 appeared to increase approximately dose-proportionally from 64-300 μg. The observed T_{max} and the apparent terminal $T_{1/2}$ following multiple QD doses were in line with the results from Day 1 and in single doses.

General PK properties (T_{max}, $T_{1/2}$, peak: trough ratio, accumulation ratio) in obese individuals with and without T2DM were generally consistent with those seen in lean individuals. However, MK-8521 exposures in obese diabetic and non-DM subjects tested in P002 and P003 were lower than those observed in the lean individuals tested in P001 and P002. Obese individuals appear to have slower absorption and higher volumes of distribution that lead to an observed lower Day 1 exposure and a higher accumulation to steady state. In addition, the slower absorption in obese individuals causes a lower peak to trough ratio and overall flatter steady state concentration profile. In general, MK-8521 exposure decreased with increasing BMI. This is generally consistent with the inverse relationship between weight and exposure reported for liraglutide [12]. This could result from the effect of BMI on the volume of distribution and slower absorption rate. The impact of BMI on volume of distribution (higher in obese subjects) also increases the observed clearance. It is also possible that adiposity results in a slower and decreased SC absorption. Preliminary population PK analysis indicates that BMI is a significant covariate impacting MK-8521 exposure, with increasing BMI being associated with reduced exposure.

Clinical Efficacy

In overweight-obese subjects with T2DM on metformin monotherapy (P003), MK-8521 doses equal to or higher than 120 μg/day over 2-4 weeks of treatment were associated with near maximal glycemic effects and were similar to doses equal to or higher than 1.2 mg liraglutide. However, due to the relatively short duration of the study and the prolonged titration period long term glycemic efficacy could not be assessed. MK-8521 appeared to lower LDL, HDL, and triglycerides relative to both placebo and liraglutide.

Due to small sample size and short duration at the maximal dose of 300μg/day, no meaningful assessment of the effect of MK-8521 on body weight could be conducted in any of the completed clinical trials. Weight loss was observed during 4 weeks of treatment with MK-8521 (during dose escalation in P003 Part II) however, the study design did not support a rigorous assessment of weight effects.

Clinical Safety

As of November 2014, single and multiple SC doses of MK-8521 have been administered to a total of approximately 118 subjects, with doses from 2-300 μg as single doses and 34-300 μg as multiple doses for up to 29 days. The majority of reported adverse experiences (AEs) have been mild to moderate in intensity. The most commonly reported AEs have been headache, dizziness, loss of appetite and gastrointestinal AEs of nausea, vomiting, diarrhea and abdominal pain/discomfort. No clinically significant glycemic abnormalities (hypo or hyperglycemia) have been reported.

Potential safety issues that have manifested in clinical testing to date include GI intolerance and HR increases. Both appear to be generally consistent with effects reported for other agents in the GLP-1R agonist class [12,13,14]. GI intolerance has manifested as adverse events (AEs) including nausea, vomiting, and abdominal pain, and was dose limiting with

single and multiple doses in lean healthy individuals. GI AEs have been encountered in subjects with T2DM, though tolerability has been generally good through the top dose tested in P003 (300µg/day). This is likely attributed to the lower exposures achieved in the obese population studied in P003, and the more extended dose escalation strategy permitting acclimation to GI effects of GLP-1R agonism.

The HR increases observed with MK-8521 have generally increased with dose. At the top tested dose in T2DM patients in P003 (300µg/day) a small, non-statistically significant higher HR (24-hour weighted mean average) was observed with MK-8521 relative to liraglutide 1.8 mg [2.46 (-1.42, 6.34) beats per minute vs. liraglutide and 9.61 (4.42, 14.81) beats per minute vs. placebo]. Greater HR increases have occurred in individuals, and several subjects in P001, 002 and 003 have been discontinued for meeting protocol pre-specified HR discontinuation criteria.

Two subjects have experienced serious adverse events (SAEs) in MK-8521 clinical studies. Both of these occurred in subjects with T2DM in P003:

- One subject with pre-existing seizure disorder (not reported on screening) experienced a seizure and supraventricular tachycardia (SVT) 2 days after early discontinuation from the study medication. The subject was randomized to MK-8521 and was discontinued on Day 2 (after dosing of 64 µg MK-8521), due to detection of a 15 minute episode of SVT on protocol-routine telemetry monitoring. Both the seizure and SVT were considered by the study investigator to be not related to study drug.
- One subject with a prior medical history of asthma and episodes of palpitation (not reported on screening) developed an SAE of pre-syncopal episode, SVT with a HR of 140-150 bpm and asthma exacerbation on the 21st day of treatment with MK-8521, two days after dose escalating from 180 µg/day to 240 µg/day. The subject was hemodynamically stable during the event. The SVT resolved with return to normal sinus rhythm after the subject was transferred to an area hospital. The SAE was rated as related to study drug by the investigator.

Cases of pancreatitis have been reported in patients taking GLP-1R selective agonists [13,14] though causality is not definitively established. No subject in MK-8521 clinical studies as of November 2014 has developed a clinical picture consistent with pancreatitis. Transient, asymptomatic increases in lipase were observed in several subjects in the three Phase I clinical trials:

- In P001, mild elevations (<2-fold ULN) in serum lipase were observed in 3 subjects after dosing at the 72 µg dose of MK-8521 level though there were no associated symptoms suggestive of pancreatitis. Subjects remained asymptomatic at subsequent follow up. Repeat lipase levels did go to near or within normal range.
- In P002, six subjects receiving MK-8521 at multiple doses ranging from 72 µg to 150 µg had an increase in lipase of <2.5 x ULN (maximum 713 IU/L; ULN=300 IU/L) between days 8 and 14 of dosing. None of these subjects had a clinical picture consistent with pancreatitis and 5 of 6 subjects levels did return to below the ULN approximately 3 to 14 days later.

- In P003, 7 subjects, had asymptomatic lipase elevations to >3-fold the laboratory upper limit of normal. Lipase elevations >3-fold the laboratory upper limit of normal were observed in 3 subjects on MK-8521, 3 subjects on placebo or pre-dose and 1 subject on liraglutide. No clear association between MK-8521 dose or duration of drug administration and lipase elevations was observed. In 2 subjects on MK-8521, lipase increased and decreased to within normal limits despite continued dosing.

Anti-drug antibody (ADA) formation may occur and result in ADAs cross reacting with endogenous peptides (GLP-1, glucagon, OXM), though the potential for ADAs to present a significant safety issue is unclear. One individual treated with MK-8521 (in P002) has developed treatment-emergent MK-8521-binding ADAs that were transient. These ADAs were found to be neutralizing in a cell based assay assessing MK-8521 activation of the glucagon receptor, and negative in a cell based assay assessing MK-8521 activation of the GLP-1 receptor.

In light of the glucose dependence of the GLP-1R glucose-lowering mechanism, the risk of hypoglycemia with GLP-1R agonist treatment is considered low in individuals not concurrently taking anti hyperglycemic agents with hypoglycemic potential (i.e., sulfonylureas, insulin). The risk is anticipated to be similarly low with MK-8521. Consistent with this, clinically significant hypoglycemia has not been detected in either healthy subjects or T2DM patients in clinical testing to date.

Other than the specific observations summarized above, there have been no important abnormalities noted in vital sign parameters, routine blood and urine chemistry, hematology, glucometer measurements, ECG or physical exams.

As of November 2014, MK-8521 is not being evaluated in ongoing clinical trials.

4.1.3 Information on Other Trial-Related Therapy

Metformin is a biguanide that is widely considered to be a first line drug for the treatment of T2DM. Subjects who are on a stable dose of metformin (≥1000mg/day) for ≥12 weeks are eligible to participate in this trial. Subjects will remain on their stable dose of metformin throughout the trial including the 14-day post-treatment visit.

Liraglutide is a glucagon-like peptide-1 receptor agonist that is DPP-4 resistant, and which has been shown to improve glycemic control in patients with T2DM [15-20]. At the present time, liraglutide is indicated for use as second-line therapy in both the United States (refer to the liraglutide package insert in Section 7) and the European Union [21].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

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.

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

The current protocol is expected to extend the experience with MK-8521, observe safety parameters and to assess the effect of multiple daily doses of MK-8521 on change from baseline in A1C and body weight after 12 weeks in subjects with T2DM. In particular, the current trial will allow for a direct comparison of the effects of MK-8521 and liraglutide on safety, tolerability as well as efficacy measured as changes in A1C and body weight.

Approximately 160 subjects with T2DM will receive MK-8521 300 μg QD, MK-8521 180 μg QD, placebo QD or open-label liraglutide QD for 12 weeks. Safety data and the effect of MK-8521 on A1C and body weight will be assessed at 12 weeks. The rationale for this approach is to examine the safety, and efficacy of MK-8521 in a larger cohort of subjects with baseline characteristics that resemble the target population for this compound, in an outpatient setting. The rationale for the duration of the study is to allow for sufficient time for glycemic efficacy to reflect changes in A1C and for significant changes in body weight to occur.

Randomization of subjects will be stratified based on baseline A1C, BMI and AHA washout status as these factors may affect the magnitude of response to therapy. Any imbalance of these characteristics between treatment arms may confound the actual treatment effect.

The rationale for including liraglutide is to provide a reference arm to better understand the efficacy observed with MK-8521 on glycemic and body weight endpoints, and on safety and tolerability (e.g., HR and GI tolerability). As previously noted, liraglutide therapy is associated with improved glycemic control, body weight loss, GI adverse events, and a 2-4 bpm increase in HR (the increase in HR was reported in Phase 3 trials and measured at trough levels). Data obtained from the liraglutide arm may help to provide information on the profile of a dual agonist of GLP-1 and GCGR (MK-8521) vs. activation of the GLP-1 receptor alone (liraglutide). Potential effects on safety parameters and weight loss that may be obtained by activation of GCGR in the context of GLP-1 activation may be highlighted by the direct comparison to the liraglutide treated cohort.

Since liraglutide is currently available only as a single use pen injector, treatment with liraglutide cannot be easily blinded in the context of a clinical trial. Liraglutide will therefore be dispensed as an open-label medication. Although blinded comparisons may be most robust, including liraglutide will still provide a useful benchmark to support the assessment of the safety and efficacy of MK-8521. This conclusion is supported by the observation that many of the Phase 3 liraglutide active-comparator studies were conducted as open-label, with no notable difference in the safety or efficacy profile relative to double-blind studies. It is also important to note that there is some variability of weight loss (and A1C-lowering) responses with liraglutide across trials—especially over the initial 3 months. This would make cross study comparisons of MK-8521 with liraglutide non-robust. Nonetheless, results obtained in the liraglutide arm will be interpreted in light of previously published liraglutide data, and with consideration of the non-blinded comparison. The primary and key secondary endpoints will focus on the comparison of MK-8521 with placebo.

To minimize confounding effects of other AHAs on assessment of safety parameters, body weight and glycemic control, only subjects on a stable dose of metformin (either at screening, or after an AHA run-in wash-off period, for subjects entering on metformin and another AHA) will be allowed to be randomized in this trial. Since this trial is the first trial

of MK-8521 conducted in subjects with T2DM in an outpatient setting, only subjects 21 to the age of 65 (inclusive) and without a history of cardiovascular disease will be allowed to participate.

A more detailed description of the study design and population is reviewed in Sections 2.1 and 2.2 of this protocol.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The selection of doses and regimens to be administered in this study is based on safety and pharmacodynamic measures obtained in P001 and P002 in healthy subjects and P003 in subjects with T2DM and obese healthy subjects and known characteristics of GLP-1 agonists. The two doses of MK-8521 studied (180 µg and 300 µg) will offer better understanding of any potential dose response relationship with regards to safety (increase in HR and GI intolerance) and efficacy (glucose reduction and weight loss) endpoints.

In P003, administration of 300 µg MK-8521 resulted in an exposure of 66.5 nMhr in subjects with T2DM. Treatment of subjects with T2DM with 300 µg/ day MK-8521 was associated with a placebo-adjusted mean increases in HR $TWA_{0\text{-}24hr}$ of ~ 8.3 bpm and a liraglutide 1.8 mg–adjusted mean increase in HR $TWA_{0\text{-}24hr}$ of ~2.46 bpm. GI AEs occurred in 15/18 (83.3%) subjects with T2DM exposed to MK-8521 in Part 2 of P003 and were generally mild. No clear relation between dose and GI AEs was identified and no discontinuations from study medication due to GI AEs occurred with MK-8521. Glucose lowering was similar between 300 µg MK-8521 and 1.8 mg liraglutide. The LS mean change in 24hr WMG with 300 µg MK-8521 was -53.4 mg/dL vs. -59.7 mg/dL with liraglutide, and the change in FPG was -52 mg/dl for both liraglutide 1.8 mg and MK-8521 300 µg. In P003, doses equal to or higher than 120µg MK-8521 and 1.2 mg liraglutide were associated with near maximal glycemic effects.

The rationale for having a higher dose and lower dose arms is primarily to study the dose-response of safety and efficacy parameters of different doses of MK-8521. The lower dose arm of 180 µg is expected to provide sufficient enhancement of glucose-dependent insulin secretion to achieve notable changes in A1C. Based on modelling and data obtained in prior studies, this dose should be well tolerated and associated with a placebo-adjusted mean increases in HR $TWA_{0\text{-}24hr}$ of ~ 7 bpm that is expected to be similar to the change in HR with liraglutide 1.8 mg. Gastrointestinal intolerance (presenting as nausea, vomiting etc.) can occur with GLP-1 agonist therapy and may be partially mitigated by dose titration [13]. In keeping with this notion, a dose escalation/titration regimen will be implemented in the current trial.

4.2.2.1 Starting Dose for This Trial

The initial MK-8521 dosing will begin at 60 µg/day (0.1 ml/day) and will be escalated up to the full dose of 180 µg/day (0.3 ml/day) no later than Day 21, and 300 µg/day (0.5 ml/day) no later than Day 28 (See Section 5.2.1.2 for dose escalation).

The rationale for the dose escalation regimen is based on gastrointestinal (GI) AE data from Phase I studies and reports of up to 40% GI adverse events (nausea and vomiting) at GLP-1 agonist therapy initiation [12]. As gradual dose-escalation of exenatide has been shown to successfully reduce the proportion of subjects experiencing dose-limiting nausea and vomiting, with no loss of glucoregulatory activity, a similar dose-escalation strategy will be employed in this trial [13].

A double-dummy approach will be used in the trial because the volume of MK-8521 administered differs between the 180 µg and 300 µg dose arms (see Table 6 in Section 5.2.1.2). With the double-dummy approach, subjects randomized to MK-8521 or MK-8521 placebo will administer 2 injections each day: 1 injection from the MK-8521 180 µg vial (Vial C) and 1 injection from the MK-8521 300 µg vial (Vial D). Subjects randomized to the MK-8521 180 µg group will also receive placebo for MK-8521 300 µg. Subjects randomized to the MK-8521 300 µg group will also receive placebo for MK-8521 180 µg. Subjects randomized to placebo will receive placebo for both 300 µg and 180 µg MK-8521. Subjects randomized to liraglutide will receive only open-label liraglutide for the duration of the study.

The initial liraglutide dosing will begin at 0.6 mg/day and will be escalated up to the full dose of 1.8 mg/day no later than Day 21.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Efficacy endpoints will be assessed after 12 weeks of daily dosing and will include change in glycemic parameters and change in body weight.

Glycemic efficacy endpoints will include the changes from baseline in A1C and FPG at Week 12. A1C reflects average glucose concentrations over the past 3-4 months and, therefore, provides a useful index of the glycemic control of treatment with MK-8521 over that time period. It is a standard efficacy endpoint used to assess the glycemic efficacy of AHAs. A1C is a key glycemic parameter which correlates with reduction of risk of diabetic microvascular complications. The measurement of FPG will provide insight into the effects of treatment with MK-8521 on this endpoint and characterize the earlier time course of glucose control in this trial.

Body weight reduction is an anticipated outcome of co-activation of GLP-1R and GCGR. Body weight loss may also drive A1C reduction at a modeled rate of 0.1% reduction in A1C for every 1 kg reduction in body weight. While the trajectory of reduction in A1C achieved with GLP-1R activation (as observed with liraglutide) reaches near maximal efficacy at 12 weeks, further potential weight loss past 12 weeks with MK-8521 may lead to further reduction in A1C. Data regarding body weight loss collected throughout the 12 week treatment period will be used to model further weight loss and subsequent A1C reduction up to 24 weeks.

Other efficacy endpoints that will be assessed include changes from baseline at Week 12 in fasting plasma lipid profile (including LDL-cholesterol, HDL-cholesterol and triglycerides), and blood pressure. These are clinically meaningful metabolic endpoints that may change

with body weight loss. Moreover, glucagon receptor activation has previously been implicated in several studies as causing a reduction in LDL-cholesterol.

Efficacy endpoints obtained from both MK-8521 arms will be interpreted vs. placebo and vs. results collected in the liraglutide-treated arm.

There exist limitations of the comparisons to liraglutide, as liraglutide will be dispensed as an open label medication and MK-8521 as blinded. Data may be confounded by subjective assessments, compliance, or other affects based upon subject and investigator knowledge of the assigned therapy in the liraglutide arm. To mitigate these effects, previously published liraglutide data will be taken into account.

4.2.3.2 Safety Endpoints

Safety assessment will include collection of adverse events (including reports of nausea, vomiting or injection site reactions), a hypoglycemia assessment log to collect information on each potential episode of hypoglycemia (including concurrent fingerstick glucose value) and physical examination including vital signs. Incidence of adverse events of symptomatic hypoglycemia is defined as a Tier 1 pre-specified safety parameter. Tier 1 pre-specified safety parameters are parameters subject to inferential testing.

Due to a potential increase in HR as detailed in section 4.1.2, HR will be monitored at all study visits. Discontinuation criteria that incorporate parameters of increase in HR [Tachycardia (HR >100 bpm) of any duration associated with symptoms, sustained resting HR >100 bpm and sustained increase from baseline in resting HR ≥30 bpm] have been outlined and provide boundaries of tolerance for increase in HR (see Section 5.9). Based on prior studies with liraglutide, it is anticipated that agonism of the GLP-1 receptor may result in a low rate of patients meeting the discontinuation criteria for an increase in heart rate. In the event of ≥5 subjects (potentially comprising over 10% of subjects in a single study arm) discontinuing blinded investigational product (MK-8521 or matching placebo) due to meeting the defined criteria for discontinuation due to an increase in HR, a review of unblinded safety data by a Standing Internal Data Monitoring Committee (siDMC) will be triggered. If a clear disparity is observed between the different study arms in the allocation of the discontinued subjects the siDMC may decide to continue or stop the study, or stop or modify the study arm. For further details on the siDMC, see the siDMC charter and Section 7.3.2.

Key endpoints for HR that will be assessed will include change from baseline at Week 12, events of sustained increase from baseline in resting HR ≥ 30 bpm from baseline, events of sustained increase in resting HR > 100 bpm and tachycardia (HR >100 bpm) of any duration associated with symptoms.

Laboratory safety studies will include blood chemistry, lipid panel, hematology, urinalysis and electrocardiograms (ECGs). Refer to Section 6.0 and Section 7.1.3.1 for further details.

Though no events of pancreatitis have occurred in subjects exposed to MK-8521, asymptomatic and transient elevations in circulating lipase were observed in a few subjects in the Phase I clinical studies. In the current study, subjects will have regular monitoring of circulating lipase levels and symptoms suggestive of pancreatitis. A discontinuation criterion that incorporates both elevated circulating lipase as well as relevant symptoms has been

outlined (see Section 5.9) and provides boundaries of tolerance for elevated circulating lipase levels.

GLP-1 receptor activation may result in increase in serum calcitonin. Circulating calcitonin levels will be monitored during the study.

As antibody-mediated immune responses to MK-8521 could occur, anti-drug antibody formation will be assessed through analysis of serum samples as noted in the Trial Flow Chart (See Section 6.0). If MK-8521-specific antibodies are confirmed to be present, additional tests will be performed to determine if the antibodies cross react with GLP-1, glucagon, or OXM. Additional testing will include titer assessment and assessment of the ability of the antibodies to neutralize the action of MK-8521 in a cell based assay.

4.2.3.3 Pharmacokinetic Endpoints

C_{Trough} will be assessed at predefined time points throughout the trial.

4.2.3.4 Planned Exploratory Biomarker Research

Understanding the relative contribution of GLP-1R activation vs. GCGR activation to the observed biologic effect may shed light on the mechanism of action of MK-8521 and facilitate its clinical development. Several biomarkers including endogenous glucagon, ketones, FGF-21 and kisspeptin have shown differential response to GLP-1R/GCGR co-agonism or GCGR agonism vs. GLP-1R agonism in preclinical models. In the current study, samples for these potential biomarkers will be collected. A decision to analyze these samples will be based on potential for utility in light of emerging clinical efficacy and safety outcomes.

Understanding the effect of MK-8521 on β-cell function and insulin resistance may shed light on its anti-hyperglycemic mechanism of action and facilitate further clinical development. Using fasting measurements of insulin, glucose and C-peptide, β-cell function and insulin resistance may be estimated using the HOMA-β and HOMA-IR calculations, respectively. In the current study, samples for insulin and C-peptide will be collected. A decision to analyze these samples will be based on potential for utility in light of emerging clinical efficacy and safety outcomes.

Understanding genetic determinants of drug response 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. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens routinely and specifically collected 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.

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 specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. 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. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects between the ages of 21 and 65 years (inclusive) with T2DM 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:

At Visit 1/Screening

1. have T2DM in accordance with American Diabetes Association guidelines [25] and be ≥21 to ≤65 years of age (inclusive) on the day of signing the informed consent form (ICF).
2. Meet one of the following criteria:
   - be on a stable dose of metformin monotherapy (≥1000 mg/day; metformin IR or metformin XR) for at least 12 weeks prior to Visit 1/Screening with a Visit 1/Screening A1C ≥7.5 and ≤10.5% (≥58 mmol/mol and ≤91 mmol/mol).
   - be on dual therapy with metformin (≥1000 mg/day: dose stable for at least 4 weeks prior to Visit 1/Screening) and a second* AHA with a Visit 1/Screening A1C of ≥7.0% and ≤10.0% (≥53 mmol/mol and ≤86 mmol/mol) and be willing to washout second AHA.

   ***Note:** Allowable AHAs are: DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides.

Note: A1C may be repeated once if the investigator's assessment is that the value is inconsistent with prior values or inconsistent with the subject's clinical status. The last laboratory draw/result should be used to assess eligibility.

3. have a body mass index (BMI) $\geq$23 kg/m^2 and $\leq$40 kg/m^2.

(BMI = weight (kg)/[height (m)]^2.)

4. have personally signed and dated the ICF indicating that he/she has been informed of all pertinent aspects of the trial.

Note: 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.

5. be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. Meet one of the following categories:

a) The subject is a male.

b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women $\geq$45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

c) The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant*:* while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- non-hormonal intrauterine device (IUD)
- vasectomy of a female subject's male partner

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-

ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

7. have a history of stable weight for at least 6 months prior to Visit 1/Screening (as determined by subject report).

Note: Weight-stable is defined as <5% change in body weight in the last 6 months.

At Visit 2/Week -2

Only for subjects for whom Visit 2/Week -2 is more than 2 weeks after Visit 1/Screening (this will include all subjects undergoing AHA washout):

8. A1C ≥7.5% and ≤10.5% (≥58 mmol/mol and ≤91 mmol/mol).

   Note: An A1C sample should **not** be drawn at Visit 2/Week -2 if this occurs within 2 weeks of Visit 1/Screening.

   Note: A1C may be repeated once if the investigator's assessment is that the value is inconsistent with prior values or inconsistent with the subject's clinical status. The last laboratory draw/result should be used to assess eligibility.

5.1.3 Subject Exclusion Criteria

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

At Visit 1/Screening

Diabetes Diagnosis and Prior Therapy Criteria

1. has a history of type 1 diabetes mellitus or a history of ketoacidosis, or subject is assessed by the investigator as possibly having type 1 diabetes mellitus confirmed with a C-peptide <0.7 ng/mL (0.23 nmol/L).

   Note: Only subjects assessed by the investigator as possibly having type 1 diabetes should have C-peptide measured at Visit 1/Screening.

2. has a history of other specific types of diabetes (e.g., genetic syndromes, secondary pancreatic diabetes, diabetes due to endocrinopathies, drug- or chemical-induced, and post-organ transplant).

3. Prior AHA use:

   - **For subjects on metformin monotherapy at screening:** treatment with anti-hyperglycemic agents (AHA) other than metformin within the last 12 weeks is an exclusion. However, these subjects may be re-screened after at least 12 weeks has passed since discontinuation of the non-metformin AHA (see exclusion criterion #5 on restrictions for prior use of GLP-1 receptor agonists).

- **For subjects taking dual therapy at screening and eligible to undergo washout:** treatment with one of the permissible AHAs (DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides) is not an exclusion.

4. is currently on or likely to require treatment with a prohibited medication (see **Section 5.5** for a list of prohibited medications).
5. has been treated with any GLP-1 receptor agonist (e.g. Byetta™, Victoza™ or investigational agents) within the last 6 months or has had a GLP-1 receptor agonist discontinued due to gastrointestinal intolerance or lack of efficacy.

   Note: treatment with a GLP-1 receptor agonist that was discontinued >6 months prior to Visit 1/screening is not an exclusion if the GLP-1 receptor agonist was discontinued for reasons other than gastrointestinal intolerance or lack of efficacy.
6. is taking a beta blocker or medications with sympathomimetic activity (e.g. pseudoephedrine, phenylpropanolamine, inhaled albuterol, methylphenidate, etc.).

   Note: Systemic and ophthalmic beta blockers are prohibited.

Concomitant Disease of Organs and Systems

7. has a history of clinically significant gastrointestinal disorder (including diabetic gastroparesis; irritable bowel disease; recurrent episodes of nausea, vomiting, diarrhea and abdominal pain).
8. has a history of clinically significant and active, immunological, respiratory, genitourinary or major neurological (including stroke, transient ischemic attack and chronic seizures) abnormalities or diseases.
9. has a history of cardiovascular disease (including diabetic cardiomyopathy) or significant cardiac condition (including a history of myocardial infarction, stable or unstable angina, arterial revascularization, pathologic, symptomatic or sustained tachyarrhythmia [e.g. atrial fibrillation, sustained supraventricular tachycardia, symptomatic non-sustained supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, Wolf-Parkinson-White syndrome, congenital long QT syndrome, etc.]) or heart failure.
10. has a history of malignancy ≤5 years prior to signing informed consent, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.

    Note (1) A subject with a history of malignancy >5 years prior to signing informed consent should have no evidence of residual or recurrent disease.

    Note (2) A subject with a history of melanoma, leukemia, lymphoma, or renal carcinoma is excluded.
11. has a family history of medullary carcinoma of the thyroid or multiple endocrine neoplasm type-2 syndrome.
12. has active diabetic proliferative retinopathy or a history of maculopathy.

    Note: subjects with non-proliferative diabetic retinopathy may be enrolled.
13. has human immunodeficiency virus (HIV) as assessed by medical history.

14. has:
    - blood dyscrasias or any disorders causing hemolysis or unstable red blood cells, or
    - clinically important hematological disorders (such as aplastic anemia, myeloproliferative or myelodysplastic syndromes, thrombocytopenia).
15. has a medical history of active liver disease (other than non-alcoholic hepatic steatosis), including chronic hepatitis B or C (assessed by medical history), primary biliary cirrhosis, or active symptomatic gallbladder disease.
16. is on a weight loss medication or has undergone bariatric surgery.
17. has undergone a surgical procedure within 12 weeks prior to signing the ICF or has planned major surgery during the trial.

    Note: A subject who has undergone minor surgery within the 8 weeks prior to **Visit 1/Screening** and is fully recovered or a subject who has planned minor surgery may participate. Minor surgery is defined as a surgical procedure involving local anesthesia
18. has donated blood or blood products within 6 weeks of **Visit 1/Screening** or who plans to donate blood or blood products at any time during the trial.
19. has participated in other studies involving investigational drug(s) (Phase I-IV) within 30 days prior to **Visit 1/Screening**.
20. has a history of acute or chronic pancreatitis of any etiology.
21. has a <u>mean</u> value for triplicate sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg (after at least a 5-minute seated rest).

    The approach to blood pressure assessment described in section 7.1.2.1 should be carefully followed.

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value can be explained by reversible cause (e.g. anxiety, recent exertion etc.), the blood pressure measurements should be repeated (in triplicate with 2 minutes between measurements) after the subject has rested for at least 10 minutes.

At the discretion of the investigator, subjects with elevated systolic and/or diastolic blood pressure levels may have blood pressure medication initiated or adjusted and continue in the trial if repeat blood pressure measurements no longer meet the exclusion criterion at Visit 3/Day 1. Any adjustments to blood pressure medication must occur prior to Visit 2/Week -2 and subjects must be on a stable regimen for at least 4 weeks prior to Visit 3/Day 1.

Subjects requiring AHA washout can have initiation or adjustment of blood pressure medication made concurrently with the AHA washout. If AHA washout is not required, the screening period (Visit 1 to Visit 2) should be extended so that subjects are on a stable regimen for at least 4 weeks prior to Visit 3/Day 1.

Investigators are encouraged to maximize blood pressure control according to current guidelines. Unscheduled visits may occur as necessary for pre-randomization blood pressure management.

22. has a mean value for triplicate sitting HR>88.

    The approach to heart rate assessment detailed in section 7.1.2.1 should be carefully followed.

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value can be explained by reversible cause (e.g. anxiety, recent exertion etc.), the HR measurements should be repeated (in triplicate with 2 minutes between measurements) after the subject has rested for at least 10 minutes. If the subject has a resting sitting HR>88 upon repeat (mean of three consecutive measurements), the subject must be excluded.

23. had an event of severe hypoglycemia with neuroglycopenia (i.e., with seizure or loss of consciousness) in the past 12 months (unless the subject was previously treated with insulin or a sulfonylurea and the event was clearly associated with their use).

24. has symptomatic hyperglycemia that, in the investigator's opinion, requires immediate initiation, adjustment, or addition of antihyperglycemic therapy.

Exclusion Criteria Based on Laboratory Abnormalities

25. has exclusionary laboratory values as listed in Table 3:

Table 3 Laboratory Exclusion Criteria

Parameter[1]	Population (if applicable)	Trial Limit for Exclusion
Creatinine	Male Female	≥1.3 mg/dL(≥115 µmol/L) ≥1.2 mg/dL (≥106 µmol/L)
Estimated glomerular filtration rate (eGFR) [2]		<60 mL/min/1.73 m^2
Alanine aminotransferase (ALT)		>2 times Upper Limit of Normal (ULN)
Aspartate aminotransferase (AST)		>2 times ULN
Thyroid-stimulating hormone (TSH)[3]		Outside laboratory normal range
Lipase		> ULN
Hemoglobin	Male Female	<12.0 g/dL (120 g/L) <11.0 g/dL (110 g/L)
Triglycerides (TG)[4]		>600 mg/dL (>6.78 mmol/L)

[1] Screening laboratories may be repeated once if the investigator's assessment is that the value is inconsistent with prior values or inconsistent with the subject's clinical status. The last laboratory draw/result should be used to assess eligibility.
[2] Calculated using the 4-variable MDRD equation.
[3] A subject excluded because of the TSH criterion may be re-screened after being on a stable thyroid-replacement regimen for at least 6 weeks.
[4] At the discretion of the investigator, subjects with elevated TG levels may have lipid-lowering medication initiated or adjusted and continue in the trial if a repeat measurement (at Visit 2/Week -2) no longer meets the exclusion criterion. Any adjustments to lipid-lowering medication must occur prior to Visit 2/Week -2 and subjects must be on a stable regimen for at least 4 weeks prior to Visit 3/Day 1. Subjects requiring AHA washout can have initiation or adjustment of lipid-lowering medication made concurrently with the AHA washout. If AHA washout is not required, the screening period (Visit 1 to Visit 2) should be extended so that subjects are on a stable regimen for at least 4 weeks prior to Visit 3/Day 1. Unscheduled visits may occur as necessary.

Other Criteria

26. has a positive urine pregnancy test.
27. is pregnant or breast-feeding, or is planning to conceive during the trial, including 14 days following the last dose of investigational product.
28. routinely consumes >1 alcoholic drinks per day or >7 alcoholic drinks per week or engages in binge drinking.

    Note (1): One alcoholic drink is defined as 5 oz. (150 mL) of wine, or 12 oz. (350 mL) of beer, or 1.5 oz. (50 mL) of 80-proof liquor.

    Note (2): Binge drinking is defined as a pattern of 5 or more alcoholic drinks (male), or 4 or more alcoholic drinks (female) in about 2 hours.
29. routinely consumes ≥480mg /day caffeine in caffeinated beverages (1 cup of coffee contains approximately 120 mg of caffeine. Refer to label of caffeinated products for individual caffeine content or the Investigator Trial File Binder (or equivalent)).
30. is currently a user of nicotine or nicotine containing products or does not agree to refrain from using nicotine during the trial, including 14 days following the last dose of investigational product.
31. is currently a user of any illicit drugs (including any marijuana use) or has a history of drug (including alcohol) abuse within approximately 5 years.
32. has other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or blinded investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.
33. is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

Visit 2/Week -2

34. has a positive urine pregnancy test.
35. has a clinically significant ECG abnormality at **Visit 2/Week -2** that requires further diagnostic evaluation or intervention (e.g., new arrhythmia or a conduction disturbance).
36. has a history of symptoms or signs during the **Visit 2/Week -2** physical exam suggestive of clinically significant diabetic autonomic neuropathy (e.g., orthostatic changes in BP defined as a sustained drop in systolic (>20 mmHg) or diastolic (>10 mmHg) BP after 1 minute and 3 minutes of standing).
37. has a ≥5% change in body weight since Visit 1/Screening.
38. has a mean value for triplicate sitting HR>88.

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value can be explained by reversible cause (e.g. anxiety, recent exertion etc.), the HR measurements should be repeated (in triplicate with 2 minutes between

measurements) after the subject has rested for at least 10 minutes. If the subject has a resting sitting HR>88 upon repeat (mean of three consecutive measurements), the subject must be excluded.

39. has exclusionary laboratory values as listed in Table 3

    Note: This applies **only** for subjects for whom Visit 2/Week -2 is >2 weeks after Visit 1/Screening (this will include all subjects undergoing AHA washout).

    Blood samples for these laboratories should **not** be drawn at Visit 2/Week -2 if this occurs ≤2 weeks of Visit 1/Screening.

Table 4 Visit 2/Week -2 Laboratory Exclusion Criteria

Parameter[1]	Population (if applicable)	Trial Limit for Exclusion
Creatinine[3]	Male Female	≥1.3 mg/dL(≥115 µmol/L) ≥1.2 mg/dL (≥106 µmol/L)
Estimated glomerular filtration rate (eGFR)[2,3]		<60 mL/min/1.73 m^2
Alanine aminotransferase (ALT)[3]		>2 times Upper Limit of Normal (ULN)
Aspartate aminotransferase (AST)[3]		>2 times ULN
Hemoglobin[3]	Male Female	<12.0 g/dL (120 g/L) <11.0 g/dL (110 g/L)
Triglycerides (TG)[4]		>600 mg/dL (>6.78 mmol/L)

[1] Visit 2/Week -2 laboratories may be repeated once if the investigator's assessment is that the value is inconsistent with prior values or inconsistent with the subject's clinical status. The last laboratory draw/result should be used to assess eligibility.

[2] Calculated using the 4-variable MDRD equation

[3] Only applicable if Visit 2/Week -2 occurs >2 weeks after Visit 1/Screening

[4] Only applicable for subjects who did not satisfy the Visit 1/Screening TG criterion

Visit 3/Randomization (Day 1)

40. has missed more than one daily dose of placebo run-in medication (i.e., 2 injections on the same day or 2 single injections on separate days). Refer to Section 7.1.1.8.7.
41. has a positive urine pregnancy test.
42. has a mean value for triplicate sitting HR>88.

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value can be explained by reversible cause (e.g. anxiety, recent exertion etc.), the HR measurements should be repeated (in triplicate with 2 minutes between measurements) after the subject has rested for at least 10 minutes. If the subject has a resting sitting HR>88 upon repeat, the subject MUST be excluded.

43. has a mean value for triplicate sitting systolic blood pressure >160 mm Hg and/or diastolic blood pressure >90 mm Hg (after at least a 5-minute seated rest).

44. has a fasting finger-stick glucose (FFSG) <130 mg/dL (7.2 mmol/L) or >260 mg/dL (14.4 mmol/L).

    Note: If the subject meets this exclusion criterion AND the investigator believes that the value is not consistent with the subject's current self-monitoring blood glucose (SMBG) values and **Visit 2/Week -2** FPG value, the subject should not be excluded at this time. This visit should be changed to an Unscheduled Visit and the subject should be rescheduled for **Visit 3/Day 1** within 7 days. Additional single-blind placebo run-in medication should be dispensed if needed. If the subject meets this FFSG exclusion criterion at the rescheduled **Visit 3/Day 1**, the subject MUST be excluded.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatment

Dose/ Potency	Drug	Dose	Route of Administration	Treatment Period[6]	Use
Placebo Run-in (all treatment groups)	Matching placebo for MK-8521 180 µg, 1.0mL **Vial A**	0.1 mL QD	Subcutaneous	0.1 mL[1] QD for 2 weeks	experimental (trial drug)
	Matching placebo for MK-8521 300 µg, 1.0mL **Vial B**	0.1 mL QD	Subcutaneous	0.1 mL[1] QD for 2 weeks	experimental (trial drug)
MK-8521 180 µg Group	MK-8521 180 µg 0.6 mg/mL, 1.0mL **Vial C**	0.1 mL QD to 0.3 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-84: 0.3 mL[3] QD	experimental (trial drug)
	Matching placebo for MK-8521 300 µg, 1.0mL **Vial D**	0.1 mL QD to 0.5 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-20: 0.3 mL[3] QD Days 21-84: 0.5 mL[4] QD	experimental (trial drug)
MK-8521 300 µg Group	Matching placebo for MK-8521 180 µg, 1.0mL **Vial C**	0.1 mL QD to 0.3 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-84: 0.3 mL[3] QD	experimental (trial drug)
	MK-8521 300 µg 0.6 mg/mL, 1.0mL **Vial D**	0.1 mL QD to 0.5 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-20: 0.3 mL[3] QD Days 21-84: 0.5 mL[4] QD	experimental (trial drug)

Dose/ Potency	Drug	Dose	Route of Administration	Treatment Period[6]	Use
Placebo Group	Matching placebo for MK-8521 180 µg, 1.0mL **Vial C**	0.1 mL QD to 0.3 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-84: 0.3 mL[3] QD	experimental (trial drug)
	Matching placebo for MK-8521 300 µg, 1.0mL **Vial D**	0.1 mL QD to 0.5 mL QD	Subcutaneous	Days 1-6: 0.1 mL[1] QD Days 7-13: 0.2 mL[2] QD Days 14-20: 0.3 mL[3] QD Days 21-84: 0.5 mL[4] QD	experimental (trial drug)
Liraglutide Group – Open-Label	liraglutide 6 mg/mL[5]	0.6 mg QD to 1.8 mg QD	Subcutaneous	Days 1-6: 0.6 mg QD Days 7-13: 1.2 mg QD Days 14-84: 1.8 mg QD	active-comparator

1. Equivalent to 10 Units in an insulin syringe.
2. Equivalent to 20 Units in an insulin syringe.
3. Equivalent to 30 Units in an insulin syringe.
4. Equivalent to 50 Units in an insulin syringe.
5. Liraglutide will be supplied locally by the trial site.
6. Treatment periods are approximate. See Section 6.0 for allowable visit windows.

The first dose of trial treatment will be administered at the trial site at Visit 3/Randomization (Day 1). All doses taken at scheduled clinic visits will be administered by the subject as a witnessed dose. Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

All supplies indicated in Table 5 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 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. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Escalation of Investigational Product

MK-8521 or MK-8521 Placebo Treatment Groups

Subjects randomized to MK-8521 or MK-8521 placebo will begin the trial (**Visit 3/Day 1**) on 0.1 mL from each vial (60 μg/day for subjects randomized to active MK-8521).

At **Visit 4/Day 7**, the dose should be increased to 0.2 mL from each vial (120 μg/day for subjects randomized to active MK-8521).

At **Visit 5/Day 14**, the dose should be increased to 0.3 mL from each vial (180 μg/day for subjects randomized to active MK-8521).

At **Visit 6/Day 21**, the dose from the MK-8521 300 μg vial (labelled Vial D) should be increased to 0.5 mL/day (300 μg/day for subjects randomized to the MK-8521 300 μg treatment group).

Note the following related to the dose escalation:

- The dose escalation regimen for MK-8521 may be modified by the investigator to appropriately manage observed GI intolerance. Specifically, the investigator may decide to delay **one** scheduled dose increase for up to 7 days based upon tolerability (e.g., GI adverse events).
- The dose from both vials of MK-8521 or MK-8521 placebo must reach 0.3 mL/day (180 μg/day for subjects randomized to active MK-8521) by Day 21.
- The dose from Vial D should reach 0.5 mL/day (300 μg/day for subjects randomized to the MK-8521 300 μg treatment group) by Day 28.
- Subjects who cannot tolerate 0.5 mL/day from Vial D may continue in the trial on 0.3 mL/day (180 μg/day for subjects randomized to active MK-8521) from each vial.
- No dose changes are allowed beyond Day 28.
- See Table 6 for guidance on dose escalation.
- An asymptomatic increase in HR that does not meet discontinuation criteria (Section 5.9) should not delay dose escalation.

The rationale for this dose escalation regimen can be found in Section 4.2.2.1.

Table 6 Dose Escalation for Subjects Randomized to MK-8521 or Placebo

Vial	Visit 3/ Day 1	Visit 4/ Day 7	Visit 5/ Day 14	Visit 6/ Day 21	Visit 7/ Day 28
MK-8521 180 µg or matching placebo[1] **Vial C**	initiate 0.1 mL/day	increase to 0.2 mL/day	increase to 0.3 mL/day[3]	continue 0.3 mL/day[3]	continue 0.3 mL/day[3]
MK-8521 300 µg or matching placebo[1] **Vial D**	initiate 0.1 mL/day	increase to 0.2 mL/day	increase to 0.3 mL/day[3]	increase to 0.5 mL/day[2,3]	If any step is delayed, the final dose of 0.5 mL/day must be reached at Visit 7/Day 28[2,3]

1. The investigator may delay one step of the dose escalation by one week; however, the dose from each vial must reach 0.3 mL/day no later than Day 21.
2. Subjects who cannot tolerate the 0.5 mL/day dose from **Vial D** may continue on a dose of 0.3 mL/day from each vial.
3. Subjects who cannot tolerate at least 0.3 mL/day from each vial should be discontinued (See Section 7.1.4.1).

Liraglutide Treatment Group

Subjects randomized to open-label liraglutide will begin the trial (**Visit 3/Day 1**) on 0.6 mg/day liraglutide.

At **Visit 4/Day 7**, the dose of liraglutide should be increased to 1.2 mg/day.

At **Visit 5/Day 14**, the dose of liraglutide should be increased to 1.8 mg/day.

The titration regimen for liraglutide may be modified to appropriately manage observed GI intolerance. The liraglutide dose should be titrated to the full target dose (1.8 mg/day) no later than Day 21. Subjects who cannot tolerate the 1.8 mg/day dose of liraglutide may continue in the trial on the 1.2 mg/day dose.

5.2.2 Timing of Dose Administration

On days without a clinic visit, MK-8521 300 µg, MK-8521 180 µg, or matching MK-8521 placebo SC injections; or open-label liraglutide will be administered in the morning at approximately the same time each day. Background metformin is to be taken as prescribed by their primary care physician. MK-8521 or matching placebo injections will be administered SC in the abdominal wall. The injection site should be rotated within the abdominal wall area.

On the days of clinic visits, subjects will take their investigational product, as well as background metformin, after all study procedures are completed.

At **Visit 2/Week -2**, subjects will enter a single-blind placebo run-in period. Subjects will be taught how to self-administer and will be expected to perform self-administration of the single-blind placebo SC injections during the 2-week single-blind placebo run-in period in preparation for the double-blind dosing period.

At **Visit 3/Day 1,** MK-8521 300 μg, MK-8521 180 μg, or matching MK-8521 placebo SC injections, or open-label liraglutide will be administered (see Section 4.2.2.1 for initial doses and Section 5.2.1.2 for dose escalation) by the subject as a witnessed dose after the completion of study procedures. Background metformin should be taken after all study procedures are completed. Investigational site staff should assure that the administration technique is appropriate, and provide additional training on study drug administration, as necessary.

Subjects will be asked to bring the remaining investigational product (used and unused vials/pens) to the clinic for review at each scheduled visit.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-8521 and placebo will be packaged identically so that blind/masking is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

The liraglutide treatment arm will be open-label therefore, the Sponsor, investigator and subject will know the treatment administered.

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

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 4 treatment arms. Subjects will be assigned randomly in a 1:1:1:1 ratio to MK-8521 300 μg, MK-8521 180 μg, MK-8521 matching placebo, or open-label liraglutide, respectively.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. A1C*: <8.5% or ≥8.5%
2. BMI*: <30 kg/m^2 or ≥30 kg/m^2
3. AHA washout status: yes or no.

*The Visit 1/Screening value will be used for stratification if Visit 2/Week -2 occurs ≤2 weeks of Visit 1/Screening. The Visit 2/Week -2 value will be used for stratification if Visit 2/Week -2 is >2 weeks after Visit 1/Screening (this will include all subjects undergoing AHA washout).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

AHAs taken by the subject at any time prior to Visit 1/Screening, and any other medications taken within 8 weeks of Visit 1/Screening, should be recorded on the appropriate electronic case report form (eCRF). The site may rely on subject report for this information. Concomitant medications taken during the trial must also be recorded. Subjects should be questioned about their use of concomitant medications at the time points indicated in the Trial Flow Chart – Section 6.0. Subjects should be instructed to contact the study investigator before initiating any prescription or non-prescription medications during study participation. If medical necessity requires initiation of a medication prior to discussion with the study investigator, the subject should communicate with the study investigator as soon as possible.

Prohibited Medications

Medications listed below are prohibited while subjects are receiving investigational product during the treatment period (see Section 5.9 - Subject Withdrawal/Discontinuation from Treatment Criteria):

1. All Antihyperglycemic Medications: with the exception of background metformin ≥1000 mg/day) and double-blind (MK-8521 or placebo) or open-label (liraglutide) study medication.
2. Corticosteroids: Treatment for ≥14 consecutive days or repeated courses of pharmacologic doses of corticosteroids.

   Note: Inhaled, nasal, and topical corticosteroids and physiological replacement doses of adrenal steroids are permitted.
3. Weight-loss Medications: Treatment with or initiation of a weight-loss medication (e.g., orlistat, phentermine, topiramate, lorcaserin) is prohibited (see Section 5.1.3).

   Note: Subjects who are on treatment with other medication(s) associated with weight changes (e.g., anti-psychotic agents) and who are weight-stable (i.e., <5% change in body weight within 6 months of **Visit 1/Screening**) at **Visit 1/Screening** are eligible to participate in the study and permitted to continue these medications during the trial.
4. Beta Blockers: Treatment with or initiation of a beta blocker is prohibited.

   Note: Systemic and ophthalmic beta blockers are prohibited.
5. Marijuana: Legal (including medicinal marijuana use) or illegal use is prohibited.
6. Medications with sympathomimetic activity: Treatment with or initiation of medications with sympathomimetic activity (e.g. pseudoephedrine, phenylpropanolamine, inhaled albuterol, methylphenidate) is prohibited

Guidance for Other Medications

The investigator or subject's physician/health care provider is permitted to make adjustments in the subject's non-AHA therapies throughout the trial if clinically warranted. Guidance for specific medications which are permitted during the study is provided below.

1. All subjects must be on a stable dose of metformin (≥1000 mg/day metformin IR or metformin XR) for ≥12 weeks prior to randomization.
2. Acetaminophen and NSAIDs may be used for minor ailments (e.g. minor injuries, osteoarthritis, upper respiratory tract infections) without prior consultation with the Sponsor Clinical Monitor. Individual acetaminophen doses should be 500 mg or less, with a total daily dose of 2000 mg or less.
3. Blood Pressure and Lipid-lowering Medications: Concomitant lipid-lowering medications are permitted. Antihypertensive medications with the exception of beta–blockers are permitted. It is preferable that doses of these medications remain stable during the double-blind treatment period.
4. Hormonal Replacement Therapy: Hormone replacement therapy are permitted, but subjects should be on stable regimens, and are expected to remain on their stable regimen while receiving blinded investigational product during the double-blind treatment period and for 14 days after the last dose of blinded investigational product.
5. Thyroid Hormone Replacement Therapy: Thyroid replacement medication (e.g., thyroxine) is permitted, but subjects should be on a stable dose for at least 6 weeks prior to **Visit 1/Screening**. Subjects who meet the TSH exclusion criterion specified in Table 3 may be re-screened after being on a stable thyroid replacement regimen for at least 6 weeks.
6. Nicotine/Nicotine products: The use of nicotine containing products is prohibited during the trial and for 14 days after the last dose of investigational product. This includes but is not limited to: cigarettes, cigars, pipes, smokeless tobacco, e-cigarettes and nicotine replacement therapies (nicotine patches, gum, inhalers, nasal sprays, topical gels, and lozenges).
7. Supplements and/or Traditional Medicines: The use of herbal supplements and other natural products should be discouraged. Subjects who do not discontinue the use of such supplements prior to **Visit 2/Week -2** should be instructed not to change the use or dose of the supplement during the trial. Subjects should be instructed not to initiate new supplements during the trial.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling.

For subjects who **do not** require AHA washout, initial dietary and exercise counseling will occur at **Visit 2/Week -2.**

For subjects who **do** require AHA washout, initial dietary and exercise counseling will occur at **Visit 1A** prior to the initiation of washout.

The subject will receive counseling on diet consistent with the American Diabetes Association.

At each subsequent visit, the subject's diet should be monitored, and counseling provided, as appropriate. Detailed dietary information will not be captured.

5.7.2. Alcohol, Caffeine and Tobacco

- Subjects will be counseled to limit alcohol use to moderate amounts (i.e., ≤1 drinks per day and no more than 7 drinks per week). One alcoholic drink is defined as 5 oz. (150 mL) of wine, or 12 oz. (350 mL) of beer, or 1.5 oz. (50 mL) of 80-proof liquor.
- Ingestion of caffeine will be prohibited for at least 10 hours prior to scheduled ECGs, HR and blood pressure determinations.
- Nicotine-containing products are prohibited during the trial.

5.7.3 Activity

Subjects will be counseled to maintain a medically appropriate, routine exercise program and consistent physical activity level during the trial. Subjects must not engage in physically strenuous exercise (for example: heavy lifting, weight training, calisthenics, and aerobics) within 48 hours before each blood sample collection for clinical laboratory tests for the duration of participation in the trial.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

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

A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent.

  (i.e., does not agree to any follow-up)

  Note: Since follow-up health status information is important to the full evaluation of any new agent in development, including MK-8521, **the investigator should determine if a subject who no longer agrees to *actively* participate (i.e., no longer attend visits at the investigational site, take blinded investigational product/open-label liraglutide, and have other study-related procedures conducted at the investigational site) is agreeable to providing additional *follow-up information* through interval telephone contacts** (with the site collecting only important health status information (e.g., SAEs). **Subjects who agree to follow-up contacts should be discontinued due to "Subject decision to stop active participation" (see 5.9 criteria "1" below), and not "withdrawal of consent."** See Section 5.9.1 for additional details about monitoring subjects who discontinue treatment with blinded investigational product/open-label liraglutide.

5.9 Subject Withdrawal/Discontinuation from Treatment Criteria

Discontinuation from treatment is "permanent". Once a subject is discontinued, he/she shall not be allowed to restart treatment. As outlined below, subjects who no longer wish to participate may be withdrawn from active participation, but followed in the trial, or withdrawn from the trial (i.e., no ongoing follow-up), as described below.

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

1. Subject's decision to stop active participation: Subject no longer agrees to actively participate in the study (i.e., take double-blind study medication/open-label liraglutide or other required concomitant study medication, attend study visits, or otherwise comply with study procedures), but agrees to allow follow-up contact. Subject will be contacted at times of regular study visits to collect status (i.e., SAEs), unless the subject specifically withdraws consent for follow-up.

   Note: If a subject indicates his or her intention to stop active participation in the trial (i.e., chooses to no longer attend visits at the investigational site, take investigational product, and have other study-related procedures conducted at the investigational site), the investigator must clarify with the subject if he/she is willing to continue in the study with contact at intervals (as described above) to provide a brief and focused update on health status (e.g., evaluate if the subject experienced any SAEs). **It will be essential for the subject to understand the importance of complete collection of information, and also the limited requirements for continuing to provide this information (i.e., a brief telephone contact occurring at the time of the originally planned study visits).** Thus, subjects may discontinue investigational product and continue in the study with telephone calls or they may indicate that they do not wish to have further contact with the site (i.e., withdrawal of consent).

2. Hyperglycemia:

   Subject meets (repeated and confirmed) glycemic thresholds specified in Table 7 for the specific time point in the trial, without a reasonable explanation (e.g., intercurrent illness or medication omission).

Table 7 Glycemic Thresholds For Discontinuation

Visit Interval	**Glycemic Thresholds** (Fasting plasma glucose [FPG])
After **Visit 3/Day 1** through **Visit 8/Week 6**:	FPG consistently >270 mg/dL (15.0 mmol/L)
After **Visit 8/Week 6** through **Visit 10/Week 12**:	FPG consistently >240 mg/dL (13.3 mmol/L)
Note: A consistent value for FPG is defined as a repeat measurement performed within 7 days of notification from the central laboratory. Site should reinforce diet/exercise counseling prior to repeat measurement.	

3. Hypoglycemia: Repeated (2 or more episodes since the prior visit) FPG or fingerstick glucose

   - <50 mg/dL (<2.8 mmol/L) with or without symptoms of hypoglycemia, or
   - ≤70 mg/dL (≤3.9 mmol/L) with symptoms of hypoglycemia, and without a reasonable explanation (such as increased physical activity or skipped meal) or with a reasonable explanation and likely to reoccur.

   Note: The investigator should make sure that the subject's glucose meter and test strips are functioning accurately and that the test procedure is being correctly performed by the subject prior to discontinuation.

4. Abnormal liver function tests meeting criteria specified below (see the Management of Subjects with Elevated Liver Enzymes [ALT or AST ≥3X ULN] guidance document in the Investigator Trial File Binder [ITFB] for additional details on management and discontinuation of investigational product for subjects with elevated liver enzymes):

   - ALT or AST ≥3X ULN with total bilirubin (TBL) ≥2X ULN and alkaline phosphatase (ALP) <2X ULN and without an established etiology; or
   - ALT or AST ≥8X ULN or ≥3X ULN with symptoms consistent with liver injury and without an established etiology; or
   - ALT or AST ≥5X ULN for 2 weeks or longer; or
   - ALT or AST ≥3X ULN and subject is unwilling or unable to undergo repeat ALT and AST testing at the frequency defined in the Management of Subjects with Elevated Liver Enzymes (ALT or AST ≥3X ULN) guidance document.

5. Elevation in circulating serum lipase ≥3X ULN that is associated with clinical evidence of pancreatitis (e.g., symptoms of nausea/vomiting, abdominal pain).

6. Parameters of Renal Function

    - Serum creatinine concentrations consistently ≥1.5 mg/dL (133 μmol/L) in men or ≥1.4 mg/dL (124 μmol/L) in women.
    - eGFR consistently <45 mL/min/1.73 m^2 (MDRD formula).

    Note 1: A consistent value is defined as a repeat measurement performed within 7 days of notification from the central laboratory.

    Note 2: If the eGFR or serum creatinine value continues to meet discontinuation criterion but demonstrates improvement relative to the prior result, an additional repeat may be performed (within 7 days). If this repeat continues to meet the discontinuation criteria, the subject must be discontinued from investigational product.

7. Has HR increases as detailed below:

    Note: Heart rate assessments are based on mean of three consecutive values assessed as detailed in Section 7.1.2. See Section 7.1.2 for detailed HR monitoring instructions

    - Tachycardia (mean sitting HR >100 bpm) of any duration associated with symptoms that the study investigator considers potentially related to cardiac ischemia, congestive heart failure and/or hemodynamic compromise. Concerning symptoms might potentially include chest discomfort, chest pain, shortness of breath, and/or lightheadedness.

      Note: Subjects with a minimally symptomatic event, non-sustained or recurrent, not meeting other criteria may be continued.

    - Sustained mean resting HR >100 bpm measured in the sitting position (sustained defined as continuing after 30 minutes and after 60 minutes of rest in a sitting position: if the 30-minute mean HR is <100, reassessment after 60 minutes should not be done, and reassessment should be performed after 24 hours (see note below)).

      Note: If mean HR >100 and ≤120 or if HR decreases during the 30 minute (or 60 minute) follow up to <100 bpm the dose of investigational product may be administered and the subject will be asked to return for repeat measurement within 24 hours. If mean HR is still >100 after 24 hours, the subject should be discontinued from the study medication.

    - Sustained increase from baseline in mean resting HR ≥30 bpm measured in the sitting position (sustained defined as continuing after 30 minutes and after 60 minutes of rest in a sitting position) that persists for ≥2 weeks. If the 30-minute mean HR is <30 bpm higher than baseline, the 60-minute repeat does not need to be performed and the subject may continue in the trial.

Note: An ECG should be conducted if a subject is suspected of meeting one of the HR discontinuation criteria detailed above. The ECG should be interpreted by the PI to confirm the measured HR and to diagnose any potential cardiac rhythm or rate abnormality. If confirmed, the discontinuation visit should be performed including an ECG.

8. Requirement for one of the prohibited medications listed in Section 5.5.
9. Develops any condition for which metformin is contraindicated.
10. For subjects randomized to MK-8521 or placebo, subject cannot tolerate at least 0.3 mL from each vial (i.e., 180 μg/day dose for subjects on active MK-8521). For subjects randomized to open-label liraglutide, subject cannot tolerate at least 1.2 mg/day dose.
11. For subjects randomized to open-label liraglutide, develops any condition for which liraglutide is contraindicated.
12. Pregnancy

    Note: A positive urine pregnancy test requires immediate interruption of blinded investigational product until serum β-hCG can be performed and found to be negative. If pregnancy is confirmed by a positive serum pregnancy test, subject must be permanently discontinued, and pregnancy should be reported and followed per Section 7.2.2.
13. Any medical condition or personal circumstance which, in the opinion of the investigator, exposes the subject to risk by continuing investigational product or study procedures or does not allow the subject to adhere to the requirements of the protocol.
14. Subject undergoing bariatric surgery.
15. For subjects randomized to double-blind investigational product (i.e., MK-8521 or matching placebo), the investigator or subject becomes unblinded to the subject's treatment assignment (i.e., through the IVRS system or emergency unblinding call center).

The Sponsor should be contacted immediately when a subject is discontinued from investigational product or investigational product is interrupted because of any SAE or AE assessed by the investigator as related to investigational product or laboratory abnormality assessed by the investigator as related to investigational product. The Sponsor should also be immediately contacted when a subject is discontinued from investigational product due to HR criteria (see Section 7.2.3.2 for reporting of Events of Clinical Interest).

In this trial, a subject may discontinue investigational product for any of the reasons listed above (items #1 through 15) but continue to participate in the trial (with follow-up contacts), as long as the subject does not withdraw consent. Follow-up procedures for subjects who discontinue investigational product are described in Section 5.9.1.

5.9.1 Monitoring Subjects Who Discontinue Investigational Product (Blinded or Open-Label)

If the subject withdraws consent from participating in the trial, including specifically refusing further follow-up, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before the subject's withdrawal of consent.

Subjects who discontinue treatment with investigational product (blinded or open-label) for reasons other than withdrawn consent should attend the clinic for a **Discontinuation Visit** followed by a post-treatment visit 14 days after the last dose of investigational product. Thereafter, subjects will be followed by telephone contacts according to the study visit schedule until the end of the trial (Week 12), but will not have the other procedures listed in the trial flow chart. The purpose of the telephone contacts is to collect information about subjects' health status (e.g., evaluate if the subject experienced any SAEs).

Subjects who meet criteria for discontinuation of investigational product should have the 14-day post-treatment study visit and continued follow-up contacts at the time of originally planned study visits, as described above *but will not undergo procedures outlined in the trial flow chart* (see Section 6.0).

Subjects who discontinue investigational product but who continue to participate in the trial by providing follow-up information can have medical and diabetes management by their managing physician or investigator, as appropriate. These subjects may initiate any other therapy as needed (previously prohibited medication will not apply to them). Procurement of other AHAs, including background metformin, is the responsibility of the subject.

If the trial site loses contact with the subject, the site should make at least three attempts for a telephone contact. If the three attempts of telephone contact are unsuccessful, the site should make at least two attempts to reach the subject via certified letter. All attempts to contact a subject and information received during contact attempts must be documented in the subject's medical record. If attempts to contact the subject via telephone contacts and certified letters are unsuccessful, alternative measures should be implemented, which may include contacting family members and health care providers and, when applicable, using subject location services. **In any circumstance, every effort should be made to document subject outcome, if possible.**

5.10 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.11 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, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.12 Clinical Criteria for Early Trial Termination

The trial may be terminated early based on evaluation by the siDMC if pre-specified criteria for safety-targeted siDMC review are met (refer to Section 8.2.9). Additionally, if futility criteria are met at the planned interim analysis with regards to A1C and body weight the decision may be made to terminate the study early (refer to Section 8.2.9).

6.0 TRIAL FLOW CHART

Trial Period:	Screening		Run-In	Random-ization	Treatment							Post-Treatment	
Visit Title	Screen-ing	Wash-out	Run-in	Random-ization	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12	Discontinu ation Visit	Follow-up Day 14
Visit Number	1	1A[w]	2	3	4	5	6	7	8	9	10	Discontin-uation	14-Day Post Treatment Follow-Up Visit[b]
Scheduled Week		-10	-2 (Day -14)	0 (Day 1)	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	6 (Day 42)	9 (Day 63)	12 (Day 85)	At time of discontin-uation[a]	14 days after last dose
Suggested Visit Window				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days
Administrative Procedures													
Informed Consent[c]	X												
Informed Consent for Future Biomedical Research[d]	X												
Assignment of Screening Number	X												
Contact IVRS system	X		X	X	X	X	X	X	X	X	X	X	
Subject Identification Card	X												
Assignment of Randomization Number				X									
Inclusion/Exclusion Criteria	X		X	X									
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	
Review use of any prohibited medications, including AHAs; counsel subjects on importance of not taking other AHAs[aa]	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and Activity Counseling/Monitoring[f]		X	X	X	X	X	X	X	X	X			

Trial Period:	Screening		Run-In	Random-ization	Treatment							Post-Treatment	
Visit Title	Screen-ing	Wash-out	Run-in	Random-ization	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12	Discontinu ation Visit	Follow-up Day 14
Visit Number	1	1A[w]	2	3	4	5	6	7	8	9	10	Discontin-uation	14-Day Post Treatment Follow-Up Visit[b]
Scheduled Week		-10	-2 (Day -14)	0 (Day 1)	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	6 (Day 42)	9 (Day 63)	12 (Day 85)	At time of discontin-uation[a]	14 days after last dose
Suggested Visit Window				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days
Dispense Hypoglycemia Assessment Log (HAL) and Instruct on Hypoglycemia Symptoms and Management		X	X[y]										
Dispense Glucose Meter, Fingerstick Glucose Logs, and Provide SMBG Instruction		X	X[y]										
Telephone Contact Between Clinic Visits[g]			X----------X										
Investigational Product													
Washout Second AHA[w]. Continue Metformin Monotherapy. Do Not Change Metformin Dose		X											
Instruct Self-Administration Of Medication[h]			X	X	X	X	X						
Dispense Single-Blind Placebo Run-in			X										
Dispense Double-Blind Investigational Product / Open-Label Liraglutide				X	X	X	X	X	X	X			
Witness Dose of Blinded Investigational Product / Open-Label Liraglutide in Clinic[i]			X	X	X	X	X	X	X	X			

Trial Period:	Screening		Run-In	Random-ization	Treatment							Post-Treatment	
Visit Title	Screen-ing	Wash-out	Run-in	Random-ization	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12	Discontinu ation Visit	Follow-up Day 14
Visit Number	1	1A[w]	2	3	4	5	6	7	8	9	10	Discontin-uation	14-Day Post Treatment Follow-Up Visit[b]
Scheduled Week		-10	-2 (Day -14)	0 (Day 1)	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	6 (Day 42)	9 (Day 63)	12 (Day 85)	At time of discontin-uation[a]	14 days after last dose
Suggested Visit Window				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days
Assess Trial Medication Compliance. Collect Unused and Used Investigational Product / Open Label Liraglutide[g]				X	X	X	X	X	X	X	X	X	
Clinical Procedures/Assessments													
Demographics and Medical History	X												
Height	X		X										
Body Weight	X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs (HR and Blood Pressure)[j]	X		X	X	X	X	X	X	X	X	X	X	X
Postural Blood Pressure/HR[k]			X										
Full Physical Examination (excluding rectal and urogenital examination)			X										
Brief Physical Examination[l]				X					X		X	X	
12-Lead ECG[m]			X	X							X	X	
Fasting Fingerstick Glucose in Clinic				X									
Review of SMBG Measurements and HAL				X	X	X	X	X	X	X	X	X	
Adverse Events Monitoring		X----------X										X	X

Trial Period:	Screening		Run-In	Random-ization	Treatment							Post-Treatment	
Visit Title	Screen-ing	Wash-out	Run-in	Random-ization	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12	Discontinu ation Visit	Follow-up Day 14
Visit Number	1	1A[w]	2	3	4	5	6	7	8	9	10	Discontin-uation	14-Day Post Treatment Follow-Up Visit[b]
Scheduled Week		-10	-2 (Day -14)	0 (Day 1)	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	6 (Day 42)	9 (Day 63)	12 (Day 85)	At time of discontin-uation[a]	14 days after last dose
Suggested Visit Window				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days
Laboratory Procedures/Assessments													
FPG	X		X	X	X	X	X	X	X	X	X	X	
A1C[n,x]	X		X[x]	X					X	X	X	X	
Fasting C-peptide[o]	X												
Lipid Panel[p]				X							X	X	
Chemistry Panel	X		X[x]	X				X		X	X	X	X
Hematology	X		X[x]	X				X			X	X	X
Fasting Triglycerides	X		X[z]										
Serum Lipase	X			X				X			X	X	
Serum Calcitonin Level				X							X	X	
Fasting Insulin (potential analysis, for archive) and C-peptide[q]				X							X	X	
Immunogenicity Assay (Anti-drug AB)				X				X			X	X	X
Glucagon receptor activation biomarkers (including ketones, Glucagon, FGF-21 and Kisspeptin) (potential analysis, for archive)[r]				X	X	X		X	X		X	X	
Plasma PK Sample for MK-8521[bb]					X	X	X	X	X	X	X		
Plasma PK Sample for Liraglutide (potential analysis, for archive)[s, bb]					X	X	X	X	X	X	X		
Urine Collection for Dipstick/Urinalysis[t]	X			X							X	X	

Trial Period:	Screening		Run-In	Random-ization	Treatment							Post-Treatment	
Visit Title	Screen-ing	Wash-out	Run-in	Random-ization	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12	Discontinu ation Visit	Follow-up Day 14
Visit Number	1	1A[w]	2	3	4	5	6	7	8	9	10	Discontin-uation	14-Day Post Treatment Follow-Up Visit[b]
Scheduled Week		-10	-2 (Day -14)	0 (Day 1)	1 (Day 7)	2 (Day 14)	3 (Day 21)	4 (Day 28)	6 (Day 42)	9 (Day 63)	12 (Day 85)	At time of discontin-uation[a]	14 days after last dose
Suggested Visit Window				+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days	+/- 3 days		+/- 3 days
Urine Pregnancy Test (women of childbearing potential only)[u]	X		X	X			X		X	X	X	X	
Plasma and Serum for Future Biomedical Research[d]				X					X		X	X	
Blood (DNA) for Genetic Analysis[e]				X									

a. Subjects who discontinue taking investigational product prematurely (without withdrawal of consent) should complete procedures for the Discontinuation Visit and perform the 14-Day Post-Treatment Visit two weeks following the last dose. These subjects will also be contacted via telephone by the investigator/qualified designee according to the same schedule as if the subject were still taking investigational product to collect SAEs (see Section 5.9.1).
b. The 14-Day Post-Treatment Visit should be completed 14 days after the last dose of investigational product to collect body weight, vital signs, chemistry, hematology, immunogenicity assay, and SAEs.
c. A subject ICF must be signed before any trial procedures are performed and may be signed prior to **Visit 1/Screening**.
d. The Future Biomedical Research (FBR) informed consent must be obtained before FBR samples for plasma and serum are collected. The plasma and serum samples for FBR should be collected at **Visit 3/Day 1** (pre-dose), **Visit 8/Week 6**, and **Visit 10/Week 12** (or Discontinuation Visit). For the FBR serum and plasma, samples should be collected at all time points, even if the pre-dose or other time point was not collected.
e. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
f. Eligible subjects will be seen by a dietician or qualified healthcare professional for dietary and exercise counseling at **Visit 2/Week -2** (for subjects who do not require AHA washout) or at **Visit 1A/Washout** (for subjects requiring AHA washout); follow-up at subsequent visits may be done by other appropriate site personnel evaluating the subject.
g. Telephone contact by the investigator/qualified designee will be made on Day -7 and at the midpoint between treatment visits (from Visit 3 to Visit 10) to assess for adverse events and compliance to study drug administration. Subjects who are found to be <100% compliant should be contacted by the investigator/qualified designee at least twice per week until compliance improves. Unscheduled visit(s) may be performed as needed if the subject requires retraining on study drug administration. Assessment of compliance to study medication should include subject report, used vial count (or used pens for subjects randomized to liraglutide), an estimation of vial volume as compared to an unopened vial.
h. At **Visit 2/Week -2**, subjects will be taught self-administration of placebo for MK-8521. Subjects will be expected to self-administer during the 2-week run-in period in order to develop proficiency in self-administration. Telephone contact will be made on Day -7 to assess for compliance with self-administration and adverse events. Re-instruction to be provided by clinical staff on **Visit 3/Day 1** and as appropriate. Subjects on open-label liraglutide will be taught self-administration of liraglutide on **Visit 3/Day 1**.
i. The witnessed self-administered dose will be taken after completion of all procedures for the trial visit, including the collection of all fasting blood samples.
j. Sitting triplicate blood pressure and heart rate should be collected as instructed in Section 7.1.2.1.
k. Supine and standing blood pressure and heart rate should be collected as instructed in Section 7.1.2.2.
l. Brief physical examination includes assessment of heart, lungs, abdomen, skin and extremities.
m. **Visit 2/Week -2** ECG is read locally at the investigative site. ECG for all other time points should be submitted to be read centrally.
n. A1C should not be drawn if Discontinuation Visit occurs within 4 weeks after **Visit 3/Day 1**.
o. Fasting C-peptide at Visit 1/Screening is only for subjects assessed by the investigator as possibly having T1DM.
p. Includes total cholesterol, high-density lipoprotein (HDL-C) cholesterol, low-density lipoprotein (LDL-C) cholesterol, triglycerides, non-HDL cholesterol, and apolipoprotein A-I at all time-points. Apolipoprotein A-I will only be measured if the results are considered important for future dual peptide programs.
q. Fasting insulin and C-peptide samples are to be collected in <u>all</u> study subjects at **Visit 3/ Day 1** and **Visit 10/Week 12** (or the **Discontinuation Visit**), and these, along with fasting glucose values, will be used to calculate HOMA-β and HOMA-IR. Fasting insulin will only be measured if the results are considered important for future dual peptide programs. Due to sample stability, C-peptide samples will be analyzed as they are received by the central laboratory but the results will not be provided to the site.
r. Glucagon receptor activation biomarkers will only be measured if the results are considered important for future dual peptide programs.
s. Liraglutide PK will only be measured if the results are considered important for future dual peptide programs.
t. If dipstick (midstream urine specimen) is positive for blood, WBC (e.g., leukocyte esterase, nitrites), or protein, then a urine sample for a complete urinalysis (dipstick and microscopy) should be sent to the central laboratory.
u. Women of childbearing potential will have a urine pregnancy test (and serum pregnancy test if required by site's Institutional Review Board [IRB]/Ethics Committee [EC]). Subjects with a positive urine pregnancy test during the treatment period will interrupt investigational product and undergo a serum pregnancy test.
v. Subjects on metformin monotherapy who meet all **Visit 1/Screening** eligibility criteria can proceed directly to **Visit 2/Week -2**. Subjects on metformin monotherapy who meet all Visit 1/Screening eligibility requirements except for TG and/or blood pressure criteria should have initiation or adjustment of lipid-lowering/blood pressure medication made prior to Visit 2/Week -2, with unscheduled visits, as needed. The screening period (Visit 1 to Visit 2) should be extended so that subjects are on a stable regimen for at least 4 weeks

prior to Visit 3/Day 1.

w. Only subjects who are on dual therapy with metformin and a second AHA will perform **Visit 1A/Washout**. Allowable AHAs for washout at **Visit 1A/Washout** include: DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides.

x. Performed at **Visit 2/Week -2** only if **Visit 2/Week -2** occurs >2 weeks after **Visit 1/Screening**.

y. Not applicable for **Visit 2/Week -2** if these items were already dispensed/performed at **Visit 1A/Washout**.

z. Only applicable for subjects who did not satisfy the Visit 1/Screening TG criterion. A fasting TG sample should not be obtained for subjects who satisfied the Visit 1/Screening TG criterion.

aa. Subjects should be reminded to not to take any other AHA medications other than metformin and randomized therapy (MK-8521/placebo or open-label liraglutide) during their participation in the study. They should be counseled that if another physician prescribes such a treatment (i.e., any AHA), the subject and/or the prescribing physician should immediately contact the investigational site prior to initiation of such therapy (unless alternative AHA therapy is considered clinically to be immediately required). Subjects who were washed off of another AHA should be reminded to remain off this agent while participating in the current trial, and to not re-start this agent post-study unless advised by their diabetes care-giver (whether the investigator or another physician).

bb. Subjects randomized to Liraglutide should only have PK samples for Liraglutide obtained and sent to the central laboratory (PK samples for MK-8521 should not be obtained). Conversely, subjects randomized to MK-8521/placebo should only have PK samples for MK-8521 obtained and sent to the central laboratory (PK samples for Liraglutide should not be obtained).

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.

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/ERC 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.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The use of tobacco should be collected as a part of the medical history.

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. AHAs taken by the subject at any time prior to Visit 1/Screening and any other medications taken within 8 weeks of Visit 1/Screening should be recorded on the appropriate eCRF. The site may rely on subject report for this information.

7.1.1.5.2 Concomitant Medications

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

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 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 Randomization Number

All eligible subjects will be randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a 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 randomization number.

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

Adherence to treatment will be assessed by subject report (facilitated by site review of returned used vial count (or used pens for subjects randomized to liraglutide), an estimation of vial volume as compared to an unopened vial and inspection of injection sites on the abdominal wall) during the double-blind treatment period. Every effort will be made to maintain adherence as close to 100% as possible.

Interruptions from the protocol specified treatment for >= 2 days OR compliance <= 90% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

7.1.1.8.1 Diet and Exercise Counseling and Monitoring

Refer to Section 5.7 for further details.

7.1.1.8.2 Dispense Hypoglycemia Assessment Log and Instruct on Hypoglycemia Symptoms and Management

The activities in this section will occur at **Visit 2/Week -2** for subjects who <u>are not</u> undergoing washout. They will occur at **Visit 1A/Washout** for subjects who <u>are</u> undergoing washout.

The site will review the symptoms and management of hypoglycemia with the subject. The site will counsel the subject to immediately perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), but also to avoid delay in treating these symptoms.

The subject will be instructed to complete the Hypoglycemia Assessment Log (HAL) for any symptomatic episodes he or she believes may represent hypoglycemia. If a fingerstick glucose has been obtained before or shortly (i.e., within a few minutes) after treating, the value should be recorded in the log. In addition, subjects will be instructed to record in the log any fingerstick glucose values ≤70 mg/dL (3.9 mmol/L) regardless of the presence of symptoms.

Subjects should be instructed to contact the investigational site to report:

- Any episode of hypoglycemia for which assistance was required (i.e., severe hypoglycemia).
- Any episode of fingerstick glucose ≤70 mg/dL (3.9 mmol/L) with or without symptoms.

  Note: As indicated, subjects will record symptoms and/or fingerstick glucose measurements that they believe are related to hypoglycemia on the HAL. Each episode should be evaluated by the investigator. For episodes determined to be hypoglycemia (symptomatic or asymptomatic), and for all glucose values ≤70 mg/dL (3.9 mmol/L) regardless of whether they are considered an adverse event, the Hypoglycemia Assessment (HA) eCRF must also be completed. Each event of symptomatic hypoglycemia must be reported as an adverse event on the adverse eCRF. Each episode

of asymptomatic hypoglycemia considered by the investigator to be an adverse event should also be reported on the adverse event eCRF (see Section 7.1.2.10.2.1 for guidance on reporting).

7.1.1.8.3 Dispense Glucose Meter and SMBG Instructions

The activities in this section will occur at **Visit 2/Week -2** for subjects who <u>are not</u> undergoing washout. They will occur at **Visit 1A/Washout** for subjects who <u>are</u> undergoing washout.

Glucose meters and Fingerstick Glucose Logs will be supplied to all subjects in order to perform SMBG. Subjects will be instructed on the procedure to perform fingerstick glucose measurements. Subjects will monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator (based upon his/her assessment of the subject's risk of increasing glucose concentrations) **with a minimum of two fasting determinations per week**.

From the time the glucose meters are supplied, through Visit 3/randomization, subjects should be counseled to contact the trial site if fasting fingerstick glucose levels are above 260 mg/dL (14.4 mmol/L) ≥2 times per week. Subjects will also be instructed to contact the site if their fingerstick glucose values are ≤70 mg/dL (≤3.9 mmol/L).

Furthermore, in order to assess the need for discontinuation from investigational product, subjects should be instructed to contact the site for fasting fingerstick glucose values that are >270 mg/dL (15.0 mmol/L) after Visit 3/Randomization (Day 1) through Visit 8/Week 6, or >240 mg/dL (13.3 mmol/L) after Visit 8/Week 6 through Visit 10/Week 12.

7.1.1.8.4 Witnessed Dosing

Administration of investigational product (blinded or open-label) will be witnessed by the investigator and/or trial staff at **<u>all</u>** clinic visits (when investigational product administration is continuing) after completion of all trial procedures including the collection of all fasting blood samples.

7.1.1.8.5 Dispense Single-Blind Placebo Run-in Investigational Product

Subjects will be dispensed single-blind investigational product (MK-8521 300 μg and MK-8521 180 μg matching placebos) at **Visit 2/Week -2** and instructed to take one injection (0.1 mL) per day from each vial at approximately the same time of day in the morning. The last dose of placebo run-in should be taken on the day prior to **Visit 3/Day 1**.

Refer to Section 5.2.2 for further details.

7.1.1.8.6 Dispense Double-Blind/Open-Label Investigational Product

Subjects will be dispensed double-blind investigational product at all treatment visits from **Visit 3/Day 1** through **Visit 9/Week 9**. Open-label liraglutide can be dispensed such that the subject will not run out prior to the next trial visit. Suggested liraglutide dispensing guidance can be found in Table 8.

Table 8 Suggested Liraglutide Dispensing Guidance

Visit #/Week # (window)	# of Liraglutide Pens Dispensed
Visit 3/Day 1 (14 days)	1[a]
Visit 5/Week 2 (7 days)	1
Visit 6/Week 3 (7 days)	1
Visit 7/Week 4 (14 days)	2
Visit 8/Week 6 (21 days)	3
Visit 9/Week 9 (21 days)	3
[a] One 18-mg pen is sufficient (0.6 mg x 6 days + 1.2 mg x 7 days = 12 mg used) to cover the liraglutide titration period (Visit 3 to Visit 5).	

Subjects randomized to MK-8521 (either dose) or placebo should be instructed to take one injection subcutaneously per day **from each vial** in the morning at approximately the same time each day.

Subjects randomized to liraglutide should be instructed to take one injection subcutaneously per day in the morning at approximately the same time each day.

Refer to Section 5.2.2 for further details.

7.1.1.8.7 Medication Compliance Monitoring

Subjects will be directed to bring all vials/pens (used and unused) to each visit. The investigator must maintain a complete and current accountability record for the investigational product.

Compliance with the placebo run-in medication should be monitored by study personnel at the site at the end of the placebo run-in at Visit 3/Day 1. Compliance should be assessed by all of the following:

1. subject report
2. used vial count
3. estimation of used vial volume (when compared to an unused vial).

Subjects who miss more than one daily dose (i.e., 2 injections on the same day or 2 single injections on separate days) of the placebo run-in medication are ineligible for randomization.

During the remainder of the trial, compliance with blinded investigational product will be assessed using the same approach noted above: (1) subject report, (2) used vial count and (3) estimation of vial volume as compared to an unopened vial.

For subjects randomized to open-label liraglutide, compliance will be assessed based on (1) subject report and (2) visual inspection of used pen(s).

Every effort will be made to maintain compliance at 100%:

- The investigator or designee will counsel subjects who report taking <100% of the prescribed investigational product following randomization.
- The investigator or designee will determine factors that resulted in <100% compliance with the investigational product and will take steps to improve compliance.
- Subjects will be counseled on the importance of taking their medication as prescribed.
- Subject counseling will be documented in source documents.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Vital Signs (Sitting Blood Pressure and Heart Rate)

Vital sign measurements include a triplicate measurement of sitting blood pressure and heart rate. Blood pressure and heart rate will be measured using an automated, oscillometric blood pressure measuring device at all visits as noted in the Trial Flow Chart - Section 6.0. Site personnel should use the same blood pressure measuring device throughout the study for each subject.

The following method should be used to record sitting blood pressure and heart rate for subjects in triplicate:

- Subjects will refrain from ingesting caffeine for at least 10 hours preceding the measurements.
- Subjects should be seated in a chair with their back supported, feet flat on the floor and arm bared (free of restrictions such as rolled up sleeves) and supported at heart level.
- The appropriate cuff size must be used to ensure accurate measurement. Each subject's cuff size should be noted in his/her source file to assure the same cuff size is used throughout the trial.
- Measurements should be taken on the same arm at each visit (preferably the non-dominant arm).
- Measurements should begin after at least 5 minutes of rest.
- The three measurements of both the blood pressure and heart rate must be taken approximately 2 minutes apart.
    - **Note:** Measurements will be collected until the 3 consecutive systolic BP readings do not differ by more than 5 mm Hg of each other and the 3 consecutive diastolic BP readings do not differ by more than 5 mm Hg of each other with the last triplicate set recorded in the eCRFs.
    - The mean (average) of the last triplicate set of BP readings (at Visit 1 and if necessary, at Visit 3) will be used to determine eligibility.

- Assessment of heart rate can be manual (rather than using an automated device); however, when done manually, heart rate must be measured in the brachial/radial artery for at least 30 seconds.
    - **Note:** Measurements will be collected until the 3 consecutive heart rate readings do not differ by more than 5 bpm of each other with the last triplicate set recorded in the eCRFs.
    - The mean (average) of the last triplicate set of heart rate readings will be used to determine eligibility (Visit 1, Visit 2, and Visit 3), baseline HR (Visit 3), and discontinuation criteria (all post-randomization visits).

Other procedures should not be performed during the time of the blood pressure and heart rate measurements.

7.1.2.2 Postural (Orthostatic) Blood Pressure and Heart Rate

Supine and standing blood pressure and heart rate will be taken in order to evaluate postural changes in blood pressure and heart rate at Visit 2/Week -2. These measurements will be in addition to the sitting blood pressure and heart rate measurements taken at this clinic visit.

Postural blood pressure changes will be measured according to the following procedure:

- Subject in supine position for a minimum of 5 minutes.
- Measure blood pressure and heart rate in the supine position in duplicate (at least 1 minute apart).
- Stand subject and measure blood pressure and heart rate in the standing position in duplicate according to the following instructions.
    - The first measurement of standing blood pressure and heart rate will be measured after at least 1 minute of standing.
    - The second measurement of standing blood pressure and heart rate will be measured after the subject has been standing for at least 3 minutes

Note: The mean supine systolic blood pressure value will be compared to the mean of the standing systolic blood pressure values obtained as noted above, in order to determine eligibility.

7.1.2.3 Body Weight

Body weight will be measured using a standardized, digital scale (provided by the Sponsor) at each of the pre-defined nominal time points outlined in the Trial Flow Chart – Section 6.0 as follows:

- Weight will be taken ***in duplicate*** throughout the trial at approximately the same time of day, after voiding (i.e., forced void) and while wearing only a gown and underwear (no street clothes, no shoes or socks). Investigator sites without access to gowns should weigh subject in light clothing.
- Subjects should be instructed to step gently onto the scale, place both feet together in the center of the scale and stand straight with eyes directed ahead. Subjects should be

instructed to stand still and not sway. Measurement will be recorded after the weight has stabilized.

- Body weight should be reported with precision to one decimal place (e.g., 0.1 kg or 0.1 lb). The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb, (1) check the subject to ensure proper positioning as indicated above and/or conduct an accuracy check on the scale as instructed below and (2) a different set of duplicate measurements must be obtained, and the 2 new measurements should be recorded in the source documents.
- Only the **final** body weight measurement should be recorded in the eCRF.

A 10-kg certified weight will be purchased by the Sponsor and sent to each investigational site. To assess the accuracy of the scale, the trial coordinator or appointed designee will weigh him or herself alone, then the weight alone, and finally, the individual together with the weight. Deviations of more than one scale division (±0.1 kg) will require corrective action and the Sponsor must be contacted. Accuracy check will be performed monthly and the record of scale accuracy must be sent to the Sponsor at the end of the trial.

7.1.2.4 Height

Height will be measured without shoes, using a stadiometer or other appropriate device.

Standing height will be assessed through maximum vertical stature for persons who can stand unassisted. Hair ornaments, barrettes, braids, jewelry, or cornrows should be moved or removed from the top of the head before the measurement is taken.

7.1.2.5 Physical Examination

A complete physical examination (excluding rectal and urogenital examination) will be performed at Visit 2/Week -2. A brief physical examination including assessment of the heart, lungs, abdomen, skin and extremities will be performed at time points noted in the Trial Flow Chart – Section 6.0. Abnormalities considered clinically significant should be reported as adverse events. Other body systems may be evaluated as per the judgment of the investigator or as needed to evaluate adverse events.

7.1.2.6 Electrocardiogram (12-lead ECG)

Single, supine 12-lead ECGs will be obtained at visits noted in the Trial Flow Chart – Section 6.0. ECG equipment with an instruction manual will be provided by the Sponsor.

- Subjects will refrain from ingesting caffeine for at least 10 hours preceding the procedure.
- 12-lead ECGs should be performed after the subject has rested quietly for **at least 10 minutes** in a supine position.

12-lead ECGs should be obtained prior to the nominal time assessment of blood pressure, and heart rate as well as prior to blood collection.

The **Visit 2/Week -2** ECG is read locally at the investigative site. ECGs for all other time points should be reviewed at the investigative site for subject safety monitoring, as well as

electronically transmitted to a central vendor for reading and interpretation centrally. The investigator is responsible for retaining all copies of the ECG reports.

Information to be reported to the investigator by the central scoring site will include the subject's demographic information, HR (BPM), overall interpretation, rhythm type, and HR intervals PR, QRS, QT, QTcB, and QTcF (msec), and any comments.

7.1.2.7 Fasting Fingerstick Glucose (FFSG)

FFSG values performed in the clinic will be used to assess exclusion criteria prior to randomization at **Visit 3/Day 1**.

7.1.2.8 Review of SMBG Measurements and Hypoglycemia Assessment Log (HAL)

SMBG measurements and the HAL will be reviewed at all clinic visits after **Visit 1A/Washout** (in subjects undergoing AHA washout), or **Visit 2/Week -2** (in subjects not undergoing AHA washout) and will be used to assess for events of hypoglycemia, and to determine need for discontinuation from blinded investigational product due to hypoglycemia.

7.1.2.9 Assess Subject for Discontinuation Based on Central Laboratory FPG

During the double-blind treatment period, FPG values obtained at the central laboratory will be used to assess if the subject meets criteria for discontinuation of investigational product. Refer to Section 5.9 for further details regarding discontinuation.

7.1.2.10 Adverse Event Monitoring

7.1.2.10.1 Hyperglycemia

A subject should be considered to have an adverse event of hyperglycemia if the subject has one or more symptoms (e.g., increased thirst, polyuria) typically associated with an increased glucose level. At the discretion of the investigator, this may be captured as an adverse event of "hyperglycemia." This diagnosis may be supported by, but does not require, results from a glucose meter or the trial central laboratory. Further, at the discretion of the investigator, an elevated blood glucose value without associated symptoms that is considered to be an adverse event may be reported as an adverse event of "blood glucose increased." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2).

7.1.2.10.2 Hypoglycemia

Based on review of the subject-completed HAL at each clinic visit to the site, the investigator must assess the glucose values as well as any symptoms of hypoglycemia reported by the subject.

7.1.2.10.2.1 Reporting Events of Hypoglycemia

All episodes considered as likely to represent symptomatic hypoglycemia by the investigator should be captured as an adverse even of "symptomatic hypoglycemia." This diagnosis may be supported by, *but does not require*, confirmatory blood glucose results (such as those

measured using a fingerstick or from a clinical laboratory sample). Further, at the discretion of the investigator, an asymptomatic blood glucose value ≤70 mg/dL (3.9 mmol/L) may be reported as an adverse event of "asymptomatic hypoglycemia." General guidance regarding the determination as to whether an event is considered to be an adverse event should be followed (see Section 7.2).

Regardless of whether an episode is considered an adverse event, the HA eCRF ***must*** be completed for the following:

- all episodes determined by the investigator to be hypoglycemia (symptomatic or asymptomatic).
- all glucose values ≤70 mg/dL (3.9 mmol/L).

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 the Lab Manual.

7.1.3.1 Laboratory Safety and Efficacy Evaluations

Laboratory tests are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Dipstick/ Urinalysis	Others
• Hemoglobin • Hematocrit • RBC Count • Platelet Count • WBC Count • Total Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes	• BUN • Serum Creatinine (eGFR calculated using the MDRD formula) • Calcium (total) • Sodium • Potassium • Chloride • Total Carbon Dioxide (Bicarbonate) • Magnesium • Phosphate • Uric Acid • AST (SGOT) • ALT (SGPT) • Alkaline Phosphatase • Total Bilirubin • Direct (conjugated) Bilirubin[a] • Indirect (unconjugated) Bilirubin[a] • Albumin • Total Protein	• pH • Protein (qual) • Blood (qual) • Ketones • Leukocyte Esterase • Nitrites • Glucose • Microscopy[b]	• TSH • C-peptide • Insulin[c] • A1C • FPG • Pregnancy Tests (where applicable) • Lipid Panel (i.e., Total Cholesterol, HDL-C, non-HDL-C LDL-C, and Triglycerides, apolipoprotein A-I[d]) • Lipase • Calcitonin • PK for MK-8521 • PK for liraglutide[d] • Immunogenicity Assay (Anti-drug AB) • Glucagon receptor activation biomarkers [including ketones (beta-hydroxybutyrate and acetoacetate), FGF-21 , glucagon and kisspeptin][d] • Blood for DNA analysis • Plasma and serum for FBR

Hematology	Chemistry	Dipstick/ Urinalysis	Others
a. Both direct and indirect bilirubin measured only when total bilirubin is greater than ULN. b. Microscopy performed if the site dipstick evaluation is positive for blood, nitrites, leukocytes and/or protein. c. Insulin will only be measured if the results are considered important for future dual peptide programs. d. Apolipoprotein A-I, PK for liraglutide, and Glucagon receptor activation biomarkers will only be measured if the results are considered important for future dual peptide programs.			

All routine study laboratory measurements will be performed by the central laboratory after an overnight fast (i.e., no food, investigational product, background metformin therapy, or drink except water and non-AHA non-investigational product as prescribed) ≥10 hours in duration.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The site will emphasize to the subject not to take their morning dose of investigational product prior to arrival at the study site on days when PK samples will be taken. On the morning of any visit that includes pharmacokinetic sampling, investigational product dosing will occur after the pre-dose sample is taken. If a subject is randomized to Liraglutide (open label), only the PK samples for Liraglutide should be obtained and sent to the central laboratory (and PK samples for MK-8521 should not be obtained). Conversely, if a subject is randomized to MK-8521/placebo only PK samples for MK-8521 should be obtained and sent to the central laboratory (and PK samples for Liraglutide should not be obtained).

Blood samples (approximately 4 mL) to provide approximately 2 mL of plasma for pharmacokinetic analysis will be collected at visits specified in the Trial Flow Chart – Section 6.0. The exact date and time of the blood draw and the date and time of the last dose of investigational product reported by the subject prior to the blood draw should be captured on the eCRF. The actual times may change, but the number of samples will remain the same.

Samples will be centrifuged at approximately 1700 g for about 10 minutes at 4°C (if a refrigerated centrifuge is not available, place sample in an ice water bath for at least 10 minutes before centrifugation). The plasma will be stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C within 1 hour of collection.

Detailed instructions for the sample collection, storage and shipment of plasma samples will be provided in the operations/laboratory manual (supplied by the central laboratory).

As part of understanding the pharmacokinetics of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method. These data will be used for internal (i.e. Sponsor) exploratory purposes and will not be included in the clinical study report.

7.1.3.3 Future Biomedical Research

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

- DNA for future research
- Plasma for future biomedical research
- Serum for future biomedical research

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment (see Section 5.9.1) prior to completion of the trial should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Discontinuation Visit should be performed at the time of 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 and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (PPD and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call-center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) 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. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.1.4.3 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 with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

Digital scale for body weight (see Section 7.1.2.3)

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 Fasting Prior to Scheduled Visits

Subjects should be counseled to fast (i.e., no food, investigational product, background metformin therapy, or drink except water and non-AHA non-investigational product as prescribed) for at least **10 hours** prior to all study visits.

Subjects who do not fast before a scheduled visit will be required to return fasting for a study visit within three days.

Subjects who have not fasted prior to **Visit 1/Screening** should obtain a fasting lipid profile and FPG at or prior to **Visit 1A/Washout** (in subjects undergoing AHA washout), or **Visit 2/Week -2** (in subjects not undergoing AHA washout) rather than Visit 1/Screening.

7.1.5.2 Scheduling Visits

At the end of each trial visit, the next trial visit should be scheduled. Every effort should be made to adhere to the visit schedule (see Trial Flow Chart – Section 6.0), and in general visits should be scheduled within ±3 days of the designated time-point to ensure subject has an adequate drug supply to comply with protocol dosing instructions. If unavoidable, a visit may be scheduled at a time outside of this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the treatment period is as close as possible to 12 weeks. Post-randomization, **visits should be scheduled relative to the date of Visit 3/Day 1**. If a visit is scheduled at a time other than the protocol designated time, **careful consideration must be given to the amount of investigational product the subject has available.**

Trial sites should phone the IVRS at each of the scheduled subject visits **(except Visit 1A/Washout which is not registered in the IVRS)** for purposes of enrollment tracking.

Visit 2/Week -2 Timing: Subjects not Requiring AHA Washout (on Metformin Monotherapy at Screening)

For subjects who do not require AHA washout and also do not require lipid-lowering and/or blood pressure medication adjustments, the duration of time between **Visit 1/Screening** and **Visit 2/Week -2** should be approximately 1 week.

If a laboratory is repeated to determine eligibility, that repeat should occur as soon as possible after the **Visit 1/Screening** results are available. The repeated result needs to be available before performing **Visit 2/Week -2**.

For subjects who do not require AHA washout but do require lipid-lowering and/or blood pressure medication adjustment, the duration of time between **Visit 1/Screening** and **Visit 2/Week -2** should be such that that the subject is on a stable regimen for at least 4 weeks prior to **Visit 3/Day 1**.

Visit 1A/Washout and Visit 2/Week -2 Timing: Subjects Requiring AHA Washout

For subjects who require AHA washout, the duration of time between **Visit 1/Screening** and **Visit 1A/Washout** should be approximately 1 week. If a laboratory is repeated to determine eligibility, that repeat should occur as soon as possible after the **Visit 1/Screening** results are available. The repeated result needs to be available before performing **Visit 1A/Washout**.

The duration of time between **Visit 1A/Washout** and the **Visit 2/Week -2** should be at least 8 weeks. For these subjects, lipid-lowering/blood pressure medication initiation/adjustment should be made concurrently with the AHA washout if necessary.

Remaining Visit Scheduling

For **Visit 3/Day 1** through **Visit 10/Week 12**: the treatment period begins at **Visit 3/Day 1**. All subsequent visits should be scheduled relative to **Visit 3/ Day 1**.

7.1.5.3 Subject Contacts

7.1.5.3.1 Adverse Event and Study Medication Compliance Telephone Contacts

Telephone contact by the investigator/qualified designee will be made at the midpoint between Visit 1A and Visit 2 (for subjects undergoing AHA washout), on Day -7 and at the midpoint between treatment visits (from Visit 3 to Visit 10) to assess for adverse events and compliance to study drug administration.

Section 7.1.1.8 summarizes the approach to assessment of compliance as well as addressing non-compliance when necessary.

7.1.5.3.2 Visit Reminders

Prior to each visit, subjects should be contacted to be reminded of:

- The date and time of next appointment.
- The requirement to fast for at least 10 hours prior to their visit.
- The recommendation to abstain from alcohol consumption and strenuous activity for 48 hours prior to their clinic visit.

- The requirement not to take investigational product and background metformin at home the morning of their visit (non-investigational products that are not antihyperglycemic medications should be taken as directed by the prescribing physician).
- The requirement to bring their investigational product, glucose meter, Hypoglycemia Assessment Log (HAL), and any collected SMBG information to the clinic.

7.1.5.3.3 Safety Follow-up Telephone Contacts

Subjects who discontinue study medication but agree to further contact, should be contacted by telephone per their normal visit schedule after the 14-Day Post Treatment Follow-Up Visit is performed. Refer to Section 5.9 and Section 5.9.1. These safety follow-up contacts are entered in the Safety Follow-up (SFF) eCRF.

7.1.5.4 Screening Visits

7.1.5.4.1 Visit 1/Screening

Subjects will be consented and screened according to **Visit 1/Screening** Inclusion/Exclusion Criteria and will receive a baseline screening number. The subject's medical history and concomitant medications will be reviewed, and vital signs, body weight, and height will be measured. For subjects assessed as eligible to participate in the trial, fasting blood and urine samples will be obtained.

Review of concomitant medications, assessment of vital signs, and adverse event monitoring will be maintained throughout the trial.

For detailed list of **Visit 1/Screening** procedures refer to Trial Flow Chart (**Section 6.0**).

7.1.5.4.2 Visit 1A/Washout

Eligible subjects on dual therapy with metformin and a second AHA will begin an 8-week AHA washout period at Visit 1A/Washout and will be scheduled for Visit 2/Week -2. Allowable AHAs for washout are: DPP-4 inhibitors, α-glucosidase inhibitors, sulfonylureas and glinides. Metformin should be continued at the Visit 1/Screening dose throughout the trial.

Subjects' prior/concomitant medications and adverse events will be reviewed. All subjects will (1) have diet/exercise counseling, (2) receive glucose meters and training in performing SMBG, and (3) receive instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the HAL.

Subjects will be instructed to monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator (based upon his/her assessment of the subject's glycemic control) **with a minimum of two fasting determinations per week.**

See sections 5.7.1 and 7.1.1.8.2 and 7.1.1.8.3 for additional information regarding dietary/and exercise counseling, HAL training and SMBG training, respectively.

7.1.5.4.3 Run-in (Visit 2/Week-2)

Subjects' prior/concomitant medications and adverse events will be reviewed. Vital signs, body weight, and height will be measured and laboratory samples will be obtained.

Note: If Visit 2/Week -2 occurs ≤2 weeks after Visit 1/Screening, it is not necessary to repeat A1C, hematology and chemistry panel tests at Visit 2/Week -2. The Visit 1 results from these assessments may be used to satisfy entry criteria (see Section 6, Trial Flow Chart).

A full physical exam, locally read 12-lead ECG and postural blood pressure and pulse will be performed.

All non-washout subjects (these subjects will not have a Visit 1A) will (1) have diet/exercise counseling, (2) receive glucose meters and training in performing SMBG, and (3) receive instruction on hypoglycemia symptoms, hypoglycemia management, and completion of the HAL.

All non-washout subjects will be instructed to monitor their fingerstick glucose concentrations with a frequency determined appropriate by the investigator (based upon his/her assessment of the subject's glycemic control) **with a minimum of two fasting determinations per week**.

Subjects undergoing AHA washout (who previously received dietary counseling/glucose meters/SMBG training/HAL training at Visit 1A) will have SMBG measurements, and HAL reviewed at Visit 2/Week -2. Appropriate die/exercise counseling will also be performed.

See sections 5.7.1 and 7.1.1.8.2 and 7.1.1.8.3 for additional information regarding dietary/and exercise counseling, HAL training and SMBG training, respectively.

Subjects who meet all enrollment criteria applicable through Visit 2/Week-2 (as detailed in Section 5.1) will enter the 2-week, single-blind, placebo run-in period. The placebo run-in may be initiated at Visit 2/Week -2 while laboratory data, including A1C, are pending, but randomization may not occur until all eligibility criteria are confirmed.

The first doses of single-blind placebo must be taken as witnessed doses in the clinic visit after completion of all **Visit 2/Week -2** procedures and fasting blood samples. Subjects will then be dispensed single-blind investigational product (MK-8521 180 μg and MK-8521 300 μg matching placebos) and instructed to take one injection (0.1 mL) per day from each vial at approximately the same time of day in the morning for two weeks prior to randomization. Subjects should be reminded to withhold single-blind investigational product on the day of **Visit 3/ Day 1**.

7.1.5.5 Treatment Period (Visit 3 through Visit 10)

7.1.5.5.1 Randomization (Visit 3/Day 1)

At **Visit 3/Day 1**, subjects who meet all trial enrollment criteria (see Section 5.1) will have all baseline laboratory tests and trial procedures performed and will be randomized in a 1:1:1:1 ratio to MK-8521 300 μg QD, MK-8521 180 μg QD, placebo QD, or open-label liraglutide QD.

Each subject will be assigned only one randomization number; assignment of a randomization number will occur only at **Visit 3/Day 1**.

Investigational product (double-blind and open-label) will be dispensed at **Visit 3/Randomization (Day 1). The first dose(s) of investigational product should be taken as a witnessed dose *after* completion of all trial procedures.**

7.1.5.5.2 Week 1 through Week 12: Treatment Period

Prior to each trial visit, subjects should be contacted and instructed to withhold investigational product and background metformin on the day of the trial visit (see Section 7.1.5.3). Subjects should continue to take their non-trial medications, as directed by their physician.

The investigational product doses must be taken sub cutaneous in the morning at approximately the same time each day. If a subject misses a dose of investigational product during the trial, they should be instructed to take it as soon as they remember unless it is time for the next dose. Subjects should be instructed not to "make up" for the missed dose by taking two doses at the same time.

Note: See **Section 5.2.2** for timing of dosing investigational product on the day of trial visits.

7.1.5.6 Follow-up Day 14: Post Treatment Visit

A clinic visit will be performed 14 days after the last dose of investigational product to collect specific laboratory measurements (see Trial Flow Chart, Section 6.0), SAEs, body weight, and vital signs (BP and HR).

7.1.5.7 Follow-up for Subjects Who Discontinue Investigational Product

Subjects who prematurely discontinue investigational product (blinded or unblinded) should be followed according to Section 5.9.1.

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.

All adverse events 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. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

In this trial, an overdose is any dose higher than the prescribed dose of MK-8521 or matching placebo and any dose higher than 1.8 mg/day of liraglutide.

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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 14 days following cessation of Sponsor's product must be reported by the investigator. 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 a cancer;
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 10 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 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the

investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require 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).

3. Any subject meeting HR discontinuation criteria (see Section 5.9).

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 10. The investigator's assessment of causality is required for each adverse event. Refer to Table 10 for instructions in evaluating adverse events.

Table 10 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; or	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 there is another obvious cause of the AE. (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.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the standing internal Data Monitoring Committee (siDMC) regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate Standing Internal Data Monitoring Committee (siDMC) will review any interim data that is triggered by prespecified safety criteria or is conducted for administrative planning purposes. The siDMC comprises members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial. The siDMC will monitor the trial at an appropriate frequency (see Section 8.1.4 and Section 8.2.9 - Interim Analyses) for evidence of adverse effects of trial treatment, as described in the detailed monitoring guidelines. In addition to the trigger based siDMC review, an interim analysis will be performed when at least 50% of the subjects have either completed Week 12 or have discontinued the study. The planned interim analysis will be performed for the purpose of determining whether interim efficacy and safety data justify continuation of the study conduct (potential termination for futility), and, if study continuation is warranted, to consider sample size re-estimation (refer to Section 8.2.9) based on assessment of variance. When an interim analysis is performed, the siDMC will review the data and provide guidance based on criteria detailed in the siDMC charter. The siDMC will determine whether the trial should continue (or other modifications, pre-specified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to trial participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

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 detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analysis

The primary and key secondary efficacy endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 11 below.

Table 11 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing Data Approach
Primary efficacy endpoint: A1C – Change from baseline at Week 12	cLDA	FAS	Model-based
Body Weight – Change from baseline at Week 12	cLDA	FAS	Model-based
Fasting Plasma Glucose – Change from baseline at Week 12	cLDA	FAS	Model-based

For the primary efficacy analyses, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [22] will be used. The cLDA model will include terms for treatment (4 arms), time, stratification factors of A1C (<8.5%, ≥8.5%), BMI (<30 kg/m2, ≥30 kg/m2) and AHA washout status (Yes, No), and the interaction of time by treatment, with the restriction of a common baseline mean across treatment groups. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

The primary comparisons for efficacy endpoints are each of the MK-8521 doses versus placebo. The primary population for all efficacy analyses will be the Full Analysis Set (FAS), comprised of all subjects who received at least one dose of trial therapy and have a baseline measurement or a post-randomization measurement.

8.1.2 Safety Analysis

The All-Subjects-as-Treated (ASaT) population will be used for safety analyses. Safety and tolerability will be assessed following a tiered approach by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG. For safety endpoints designated as Tier 1 (adverse events of symptomatic hypoglycemia), p-values and 95% CIs for between-treatment differences (each of the two doses of MK-8521 versus placebo and versus liraglutide) will be provided.

8.1.3 Power and Sample Size

Approximately 160 subjects will be randomized in a 1:1:1:1 ratio to 300 µg dose and 180 µg dose of MK-8521, MK-8521 placebo or liraglutide. After 12 weeks of MK-8521, a reduction of ≥ 0.8% in A1C and ≥ 2 kg in body weight, relative to placebo, is expected. This sample size will provide approximately 85% power to detect a true difference of 0.8% in the mean change from baseline in A1C between a MK-8521 dose and placebo at the 2-sided 0.05 significance level. The same sample size will provide approximately 87% power to detect a true difference of 2 kg in body weight between a MK-8521 dose and placebo. The same sample size will also provide approximately 88% power to detect a true difference of 30 mg/dL in FPG. The sample size may be increased as a result of the interim analysis. Details are provided in Section 8.2.9.

8.1.4 Interim Analysis

In the event of ≥5 subjects discontinuing blinded investigational product (MK-8521 or matching placebo) due to meeting the defined discontinuation criteria for an increase in HR, a review of unblinded safety data by the siDMC will be triggered. An siDMC review may also be triggered for other potentially important safety signals from the blinded ongoing

safety results identified during medical monitoring, to be detailed in a separate siDMC charter.

In addition to the trigger-based safety review, an interim analysis will be performed for the purpose of determining whether interim efficacy and safety data justify continuation of the study. If not, study termination for futility will be considered. If the study is not terminated, an additional goal will be sample size re-estimation based on assessment of variance (described in Section 8.2.9). The results of this interim analysis will be reviewed by the siDMC.

The endpoints, timing, and purpose of the interim analysis are summarized in Table 14 in Section 8.2.9. An unblinded statistician and programmer not associated with the day-to-day conduct of the study will provide unblinded information to the siDMC. The approach to the interim analysis is described in more detail in Section 8.2.9.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR. This study will be conducted as a double-blind study under in-house blinding procedures. At the end of the trial, the official, final database will be frozen and unblinded after medical/scientific review has been performed, protocol violators have been identified (if applicable), and data have been declared final and complete.

As discussed in Section 8.1.4 and Section 8.2.9, an interim analysis will be performed to assist in the MK-8521 development program planning (including earlier initiation of planning for subsequent studies of MK-8521 and/or of dual peptide back-up programs) and to terminate the study for futility or to adjust the sample size, as warranted. It is expected that most of the planned 160 subjects will have been randomized at the time of the interim analysis. Blinding to treatment assignment will be maintained at all investigational sites. Results of interim analyses will not be shared with the Investigators prior to the completion of the study. Subject-level unblinding will include an internal unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study. The results of this interim analysis will be reviewed by the siDMC. If interim data are felt to warrant consideration of administrative action with regard to other aspects of the development program or if study termination is under consideration due to meeting futility criteria, the unblinded interim data will be reviewed with additional individuals with programmatic oversight. Individuals directly involved with study conduct will not be unblinded until the end of the study.

If, after the trial has begun, but prior to any unblinding, changes are made to primary hypotheses and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). No separate Statistical Analysis Plan (SAP) will be issued for this trial.

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.2.2 Hypotheses

Objectives and hypotheses of the study are stated in Section 3.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

The primary time point of the study is Week 12.

The baseline value will be defined as the **Visit 3/Day 1** (Randomization) measurement. If this measurement is not available, the following pre-randomization measurement will be used as the baseline value.

Regimen at Visit 1/Screening	Baseline value
On metformin monotherapy (no washout)	If the Visit 3 measurement is missing, the Visit 1 measurement will be used. If neither measurement is available, the baseline value will be treated as missing
On dual therapy metformin and a second AHA (enter washout)	If the Visit 3 measurement is missing, the Visit 2 measurement will be used. If neither measurement is available, the baseline value will be treated as missing

The mapping of relative day ranges to Week is provided in Section 12.4.

8.2.3.1 Efficacy Endpoints

Primary Endpoints:

- Change from baseline in A1C at Week 12

Key Secondary Endpoints:

- Change from baseline in body weight at Week 12
- Change from baseline in FPG at Week 12

Other Secondary Endpoints

- Change from baseline and percent change from baseline in fasting lipids (including LDL-cholesterol level, HDL-cholesterol level and triglyceride level) at Week 12 Change from baseline in systolic and diastolic blood pressure at Week 12

Other Endpoints of Interest

- Change from baseline in glucagon receptor activation biomarkers (including ketones, glucagon, FGF-21 and kisspeptin)
- Change from baseline in fasting measures of insulin secretion (HOMA-β) and insulin resistance (HOMA-IR), at Week 12

8.2.3.2 Safety Endpoints

Safety and tolerability will be assessed by a clinical review of all relevant adverse experiences and monitoring variables related to blood chemistry, hematology, vital signs, and ECG.

Tier 1 safety endpoints are adverse events of symptomatic hypoglycemia (see Table 13).

Tier 2 safety endpoints include changes from baseline in HR at different time points.

Adverse events (overall summary, specific AEs, and AEs by system organ class) and PDLCs in laboratory and vital signs parameters (including proportion of subjects with HR>100 bpm or HR increase > 30 bpm) will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

8.2.3.3 Pharmacokinetics Endpoints

C_{Trough} will be assessed (see Section 4.2.3.3).

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population includes subjects who take at least one dose of study therapy and have at least one efficacy measurement either at baseline or during the treatment period. Subjects will be included in the treatment group to which they were randomized.

A secondary population for analyzing primary and key secondary efficacy endpoints at Week 12 will be the Per-Protocol (PP) population. All randomized subjects who take at least one dose of study medication, with a measurement at baseline and the time point of interest (Week 12), without the protocol deviations described below will be included in this population.

Protocol deviations used to determine the PP population are not just a repetition of the exclusion and inclusion criteria in the protocol, but a clinical assessment of deviations from the protocol-specified criteria that will either affect or confound the measures of efficacy. The following rules define protocol violators during the trial period of interest (Day 1 through Week 12) and will be used to identify such subjects prior to unblinding. Subjects with any of the following violations will be excluded from the PP population at all time points.

- **Drug compliance:** A subject will be excluded from the PP population due to low compliance if either of the following applies:
    - Compliance assessed by prime therapy records provided by the investigator in the eCRF is <90%.
    - <75% of evaluable trough PK samples have quantifiable concentrations. This criterion is applicable only to subjects in the MK-8521 and liraglutide groups.

Additionally, a site will be deemed to have low compliance and all subjects from that site (including those randomized to the placebo group) will be excluded from the PP population if either of the following applies:

- For sites with exactly 2 subjects randomized to active groups, both of these subjects have low compliance based on trough PK criterion noted above.
- For sites with 3 or more subjects randomized to active groups, ≥50% of subjects have low compliance based on the trough PK criterion noted above.

- **Use of prohibited medications**: The list of prohibited medications can be found in Section 5.5.
  - If a subject takes any prohibited antihyperglycemic medications after randomization (Visit 3/Day 1) for a total of ≥14 days or ≥7 consecutive days, he/she will be identified as a protocol violator.
  - A subject with pharmacologic doses of corticosteroid use ≥2 consecutive weeks after randomization will be identified as a protocol violator.
- **Incorrect double-blind study medications:** If a subject receives incorrect double-blind study medication for a total of ≥14 days during the trial period of interest, then he/she will be identified as a protocol violator.
- **Subjects who cannot tolerate 0.5 mL/day from Vial D:** If a subject does not tolerate the full target dose of 0.5 mL/day MK-8521 from Vial D, he/she will be identified as a protocol violator. This criterion will only be applied to subjects randomized to the MK-8521 300 µg group.

The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database and will be documented.

An additional secondary population to analyze the efficacy endpoints will be the modified FAS (mFAS). The modified FAS population is a subset of FAS population that excludes sites identified as having low compliance (as described in the drug compliance description for the PP population above).

The number of subjects included in the FAS, PP and mFAS populations may vary across endpoints due to the degree of missing data for each endpoint. Any substantial differences between conclusions based on the FAS, PP population, and mFAS population will be investigated.

8.2.4.2 Safety Analysis Populations

The all subjects as treated (ASaT) population will be the primary population for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they were randomized. Subjects who took incorrect study treatment for the entire treatment

period will be included in the treatment group corresponding to the study treatment they actually received.

Supplementary safety analyses will be performed in the modified ASaT population, which is the subset of the ASaT population that excludes sites identified as having low compliance (as described in the drug compliance description for the PP population in Section 8.2.4).

8.2.5 Statistical Methods

Statistical testing and inference methods for efficacy and safety analyses are described in Section 8.2.5.1 and Section 8.2.5.2, respectively. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6 - Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. All statistical tests will be conducted at the 2-sided 0.05 significance level.

8.2.5.1 Efficacy Analyses

To address the primary objective, the analysis of change from baseline in A1C at Week 12 will be performed using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger. This repeated measures model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The response vector consists of baseline and the values observed at each post-baseline time point. The cLDA model will include terms for treatment, time, stratification factors of A1C (<8.5%, ≥8.5%), BMI (<30 kg/m^2, ≥30 kg/m^2) and AHA washout status (Yes, No), and the interaction of time by treatment. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the mean over time. An unstructured covariance matrix will be used to model the correlation among repeated measurements and hence avoids the potential bias that could result from the use of specific structured covariance models. If the unstructured covariance model fails to converge with the default Newton-Raphson algorithm, the Fisher scoring algorithm or other appropriate methods can be used to provide initial values of the covariance parameters. In the rare event that none of the above methods yield convergence, a structured covariance such as Toeplitz can be used to model the correlation among repeated measurements. In this case, the empirical option will be used because the sandwich variance estimator is asymptotically unbiased while the model-based variance estimator can substantially overestimate or underestimate the true variance. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference. The cLDA model uses the maximum likelihood principle to estimate the parameters and account for missing data in an implicit fashion.

The primary hypothesis will be assessed by an ordered testing procedure, comparing each of the two MK-8521 doses to placebo at Week 12, using the above cLDA model. This testing procedure first tests the 300 µg dose. If a statistically significant result (i.e., $p<0.05$) is observed on the 300 µg dose, the primary hypothesis (for A1C) is considered met and then the 180 µg dose is tested. The secondary hypotheses (for body weight and FPG) will be assessed only if the primary hypothesis is met, regardless of the outcome of the 180 µg vs placebo comparison.

In the event that fewer than 75% of the subjects in the 300 µg dose group receive the full target dose, suggestive of dose-intolerance, the hypothesis test MK-8521 180 µg vs. placebo will be performed first. In this case if the 180 µg dose vs. placebo is statistically significant, the primary hypothesis (for A1C) will be considered met and then the 300 µg dose will be tested.

If success is achieved in the test of the primary hypothesis (i.e., at least one dose of MK-8521 provides significantly greater reduction in A1C relative to placebo following the testing procedure described above), then each of the MK-8521 doses will be compared to liraglutide using the same ordered testing procedure above. Continuous efficacy endpoints such as FPG, body weight, LDL-cholesterol level, HDL-cholesterol level, triglyceride level, systolic blood pressure (SBP), and diastolic blood pressure (DBP) will be analyzed using the above cLDA method described for A1C. Change and percent change from baseline in triglycerides will be analyzed using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression (RREG) approach that uses M-estimation. Because the percent change in triglycerides typically has a skewed distribution, the cLDA model which is based on the symmetric normal distribution is not appropriate.

The primary (A1C) and key secondary endpoints (FPG and body weight) will also be analyzed in the PP population using an ANCOVA model. The ANCOVA model will include treatment, stratification factors of A1C (<8.5%, ≥8.5%), BMI (<30 kg/m^2, ≥30 kg/m^2) and AHA washout status (Yes, No), and baseline value. By definition, there will be no missing outcome data in the PP population.

Key efficacy endpoints will also be analyzed in the mFAS population using the same statistical methods stated for the FAS population.

Table 12 summarizes the analysis strategy for all efficacy endpoints. The strategy to address multiplicity issues with regard to multiple treatment comparisons and multiple endpoints is described in Section 8.2.6, Multiplicity.

Table 12 Analysis Strategy for Efficacy Endpoints

Endpoint (All at Week 12)	Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary				
Change from baseline in A1C	P S S	cLDA ANCOVA cLDA	FAS PP mFAS	Model-based NA Model-based
Key Secondary				
Change from baseline in FPG	P S S	cLDA ANCOVA cLDA	FAS PP mFAS	Model-based NA Model-based
Change from baseline in body weight	P S S	cLDA ANCOVA cLDA	FAS PP mFAS	Model-based NA Model-based
Other Endpoints				
Change and percent change from baseline in LDL and HDL Change from baseline in SBP and DBP	P	cLDA	FAS	Model-based
Change and percent change from baseline in triglycerides	P	Robust Regression	FAS	Multiple Imputation
P=Primary; S=Secondary				

The following exploratory efficacy analyses may be performed. Analysis methods will be described in a separate document, as appropriate.

- Insulin secretion (HOMA-β) and insulin resistance (HOMA-IR). A decision for the analysis will be based on potential for utility in light of emerging clinical efficacy and safety outcomes.
- Glucagon receptor activation biomarkers (including ketones, glucagon, FGF-21 and kisspeptin). Analyses may be performed if the primary hypothesis is met or if the results are considered important for future dual peptide programs.
- If fewer than 75% of the subjects in the 300 μg dose group receive the full target dose, an additional analysis with pooling of subjects on 180 μg dose may be performed. Those subjects not tolerating the 300 μg dose and continuing on the 180 μg dose will be pooled with the subjects in the 180 μg dose group.
- The relationship between genetic variation and response to the treatments administered, and variation across the human genome with clinical data collected in this study may be analyzed. A decision for the analysis will be based on potential for utility in light of emerging clinical efficacy and safety outcomes.

Due to the limited duration of analyte stability in collected PK samples, it is necessary to conduct PK sample analysis on a rolling basis while the study is ongoing. Early unblinding limited to staff critical for the conduct of PK sample analyses will occur to allow PK analysis of subjects who received the drug (MK-8521) being measured. No multiplicity adjustment is being made since the conduct of the study is not dependent on the unblinding for early PK analysis. Unblinded PK data or results will not be shared with the protocol team prior to study completion and database lock.

8.2.5.2 Safety Analyses

The ASaT population and modified ASaT population will be employed for safety analyses. Safety and tolerability will be assessed following a tiered approach by clinical review of all relevant parameters including AEs, predefined limits of change (PDLC), laboratory tests, and vital signs. For all comparisons described below, each of the two doses of MK-8521 will be compared versus placebo and versus liraglutide.

The analysis of safety parameters will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons using the Miettinen and Nurminen method [23], an unconditional, asymptotic method. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CI provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event or meet PDLC criterion; all other AEs and PDLCs will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will always include zero when treatment groups of equal size

each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful measure to be used as a flagging method—to identify events of potential clinical relevance, that require additional review—and not a formal method for assessing the statistical significance of the between-group differences in AEs and PDLCs.

Table 13 summarizes the analysis strategy for safety endpoints. In addition, as some of the subjects in the MK-8521 300 µg and liraglutide arms may not get to the full target dose, sensitivity analyses including only subjects with the full dose may be performed for Tier 1 safety parameters.

Table 13 Analysis Strategy for Safety Endpoints

Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparisons	Descriptive Statistics
Tier 1	AE of symptomatic hypoglycemia	X	X	X
Tier 2[1]	Change from baseline in HR		X	X
	HR >100 bpm or HR increase >30 bpm		X	X
	AE summary measures		X	X
	Specific AEs[2], SOCs, specific confirmed CV SAEs, and PDLCs		X	X
Tier 3	All endpoints listed under Tier 2 (above) that have incidence <4 subjects in all treatment groups			X
	Additional hypoglycemia adverse event endpoints			X
	Change from baseline results (laboratory measurements, ECG, and vital signs)			X

[1] Non-continuous endpoints listed here will qualify for Tier 2 only if the incidence is ≥4 subjects in at least one of the treatment groups.
[2] Among those endpoints not pre-specified as Tier 1 endpoints.
AE=Adverse Event; CI=Confidence Interval; ECG=Electrocardiogram; PDLC=Pre-Defined Limit of Change; SAE=Serious adverse event; SOC=System Organ Class; X = results will be provided.

Analysis of Hypoglycemia

The Tier 1 analysis for hypoglycemia will include the numbers and percentages of subjects experiencing one or more adverse events of symptomatic hypoglycemia, regardless of glucose value.

The Tier 2 analysis for hypoglycemia will include the numbers and percentages of subjects experiencing one or more of each the following:

- Adverse events of hypoglycemia (symptomatic or asymptomatic), regardless of biochemical documentation.
- Adverse events of documented hypoglycemia, defined as adverse events of symptomatic hypoglycemia with a concurrent glucose measurement of <70 mg/dL (<3.9 mmol/L)

- Adverse events of severe hypoglycemia, defined as adverse events of symptomatic hypoglycemia that required assistance, either medical or non-medical, regardless of whether such assistance was obtained, and regardless of biochemical documentation. These events will be further sub-classified as:
    - Those that required medical assistance. Adverse events of symptomatic hypoglycemia that included a markedly depressed level of consciousness, loss of consciousness, or seizure will be classified as having required medical assistance, whether or not medical assistance was obtained
    - Those that did not require medical assistance (i.e., those episodes that required non-medical assistance to treat).

The Tier 3 summary of hypoglycemia will include the following, based on episodes classified by the investigator as adverse events:

- The numbers and percentages of subjects with each of the following, overall and by lowest reported glucose category (<50 mg/dL [<2.8 mmol/L], ≤70 mg/dL [≤3.9 mmol/L], >70 mg/dL [>3.9 mmol/L], or unknown). A subject's lowest glucose category will be classified as unknown only if no glucose measurements are available for that subject.
    1. any episodes (symptomatic or asymptomatic)
    2. symptomatic episodes
    3. asymptomatic episodes
- The numbers and percentages of subjects with episodes having precipitating factors
- The number of episodes per subject
- The number of each of the following (summed across all subjects). The overall summary will include an indication of whether precipitating factors were present.
    1. all episodes (symptomatic or asymptomatic)
    2. symptomatic episodes
    3. asymptomatic episodes

Categorization of episodes by glucose level will be performed based on the units (mg/dL or mmol/L) in which the glucose measurements were reported.

A summary of subjects with episodes that were reported on the hypoglycemia assessment (HA) eCRF but were not classified by the investigator as adverse events will also be provided. If a substantial number of subjects had episodes that were not classified as adverse events, then additional summaries may be provided for the Tier 3 endpoints above, including all episodes reported on the HA eCRF (i.e., not restricted to adverse events). It is expected that all symptomatic hypoglycemia episodes will be classified by the investigator as adverse events and, thus, that any episodes that are not classified as adverse events will be asymptomatic episodes.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups at baseline for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screen failure, and the primary reason for discontinuation will be displayed. Medical history and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables. In addition, the following demographic/ anthropometric, diabetes-related, and baseline efficacy variables will be summarized by treatment either by descriptive statistics or categorical tables. Depending on the variable of interest, statistics such as sample size, mean, SD, median, range and proportion will be provided.

- Continuous baseline demographic variables: age (years), weight (kg) and height (cm)
- Baseline BMI, and distribution of at baseline BMI (<25, ≥25 to <30, ≥30 to <35, ≥35 kg/m^2)
- Categorical baseline demographic variables: age (<65 years, ≥65 years), gender (male, female), and race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or Multi-Racial), ethnicity (Hispanic/Latino or not).
- Baseline A1C, and distribution of A1C at baseline (<8, ≥8 to <9, ≥9%)
- Baseline FPG
- Time since diagnosis of diabetes mellitus (years) (<5, ≥5 to <10, ≥10 years)
- AHA washout status (Yes, No)

The above summaries will be provided for all subjects who received at least one dose of study therapy.

8.2.6 Multiplicity

The Type-I error rate over the multiple treatment comparisons (i.e., two MK-8521 doses versus placebo) for the primary hypothesis will be controlled by an ordered testing procedure. This testing procedure will first test the 300 µg dose. If a statistically significant result is observed, then the 180 µg dose will be tested and the primary hypothesis test will be considered successful, regardless of the outcome of the 180 µg vs. placebo.

In the event that fewer than 75% of the subjects in the 300 µg dose group receive the full target dose, the first test of MK-8521 vs. placebo will be performed at the 180 µg dose. If the 180 µg dose vs. placebo is statistically significant, then the primary hypothesis will be considered successful.

The secondary hypotheses for body weight and FPG are deemed supportive and will only be tested if significance is achieved at the corresponding dose level for A1C.

Comparisons involving other efficacy endpoints and other treatment comparisons (MK-8521 doses vs. liraglutide) are considered supportive or exploratory and will be made at α=0.05

nominal level (two-sided) and 95% CIs will be provided. No multiplicity adjustment will be performed for these other comparisons.

From a safety standpoint, application of a multiplicity adjustment could potentially mask a safety concern. No multiplicity adjustment is planned for safety endpoints.

An interim analysis will be performed to assist in program planning, support sample size re-estimation, and support assessment of whether the study should be terminated based on an assessment of the overall data and in consideration of programmatic goals (described in Section 8.2.9). This is not a pivotal trial and the trial will not be stopped early for positive results. Therefore, no alpha adjustment will be made for this interim analysis.

8.2.7 Sample Size and Power Calculations

After 12 weeks of MK-8521, a reduction of ≥0.8% in A1C and ≥2 kg in body weight, relative to placebo, is expected.

A total of approximately 160 subjects will be randomized in a 1:1:1:1 ratio to 300 µg dose and 180 µg dose of MK-8521, placebo or liraglutide. A sample size of 40 subjects per arm will provide approximately 85% power to detect a treatment difference of 0.8% in A1C reduction at Week 12 (alpha=0.05, two-sided test). The half-width of the 95% CI of A1C is 0.52%. This calculation is based upon the following assumptions:

1. Cumulative attrition rates at Weeks 6 and 12 are 0.08 and 0.16, respectively.
2. The conditional standard deviation is 1.1%.
3. The conditional correlation between Weeks 6 and 12 is 0.76732.

The correlation between Weeks 6 and 12 is derived based on data from MK-0431 PN020. The high attrition rates are used to account for dropout risks due to the requirement of taking 2 subcutaneous injections daily and any potential AEs in this first outpatient trial of MK-8521. The SD is assumed to be 1.1% to account for more variability in patients with higher baseline A1C. The sample size of 40 subjects will be equivalent to an effective sample size of 35 subjects at Week 12, which accounts for information loss due to missing data and correlation among repeated measures and is derived using the method proposed by Lu, et al. [24].

The sample size of 40 subjects per arm will provide approximately 87% power to detect a treatment difference of 2 kg in body weight loss at Week 12. The half-width of the 95% CI of body weight is 1.23 kg. This calculation is based on the same dropout rates and correlation for the A1C and on the conditional standard deviation of 2.7 kg.

The sample size of 40 subjects per arm will provide approximately 88% power to detect a treatment difference of 30 mg/dL in FPG at Week 12. The half-width of the 95% CI of FPG is 18.9 mg/dL. This calculation is based on the same dropout rates and correlation for the A1C and on the conditional standard deviation of 40 mg/dL.

8.2.8 Subgroup Analyses

To assess whether the treatment effect at Week 12 is consistent across various subgroups, the between-group treatment effect (with a nominal 95% CI) for A1C and body weight will be estimated and plotted within each category of the following classification variables:

- Gender (female or male)
- Age (> or ≤ median)
- Stratification A1C (<8.5% or ≥8.5%)
- Stratification BMI (<30 or ≥30 kg/m^2)
- AHA washout status (Yes, No)
- Prior GLP-1 (Yes or No)

The consistency of the treatment effect will be assessed in the context of the primary efficacy analysis model. In the case of subgroups that are defined by terms that are in the primary analysis model, the term that confounds with the subgroup factor will be excluded from the subgroup analysis model. Treatment effects and nominal 95% CIs by category for the classification variables listed above will be reported as well as presented graphically. Formal statistical testing of treatment-by-subgroup interactions will not be performed for other subgroup factors.

The treatment effect across study centers will be summarized for A1C at Week 12 with descriptive statistics.

Results from the subgroup analyses should be reviewed cautiously. Because sample sizes within subgroups will be smaller than the overall study sample size, estimation may not be precise and 95% CIs will usually be wide in the subgroup analyses.

8.2.9 Interim Analyses

8.2.9.1 Triggered Safety Review for Discontinuation Due to HR

In the event of ≥5 subjects discontinuing blinded investigational product (MK-8521 or matching placebo) due to meeting the defined discontinuation criteria for an increase in HR, a review of unblinded safety data by a Standing Internal Data Monitoring Committee will be triggered. For further details on the siDMC, see Section 7.3.2. Review criteria will be provided in the siDMC charter.

8.2.9.2 Planned Efficacy and Safety Review

An interim analysis will be performed when at least 50% subjects have completed the Week 12 Visit or discontinued prior to the Week 12 Visit, to assist in program planning, support sample size re-estimation, and support assessment of whether the study should be terminated based on an assessment of the overall data and in consideration of programmatic goals. The treatment-level results will be reviewed by the siDMC. This is not a pivotal trial and the trial will not be stopped early for positive results. Therefore, no alpha adjustment will be made for this interim analysis.

If interim data are considered to warrant consideration for administrative action with regard to other aspects of the development program, the unblinded interim data will be reviewed

with additional individuals with programmatic oversight. Individuals directly involved with study conduct will not be unblinded.

For the interim efficacy analysis, the Full Analysis Set (FAS) population will be used as described in Section 8.2.4.1. Additional analyses based on the per-protocol population and the modified FAS population will be performed.

The efficacy of the MK-8521 treatment groups will be assessed using the same analysis approach described in Section 8.2.5.1 and the key endpoints are outlined in Table 14. Study termination at the interim analysis will be considered if either of the following criteria is met for both doses of MK-8521:

- A1C futility criterion: Potentially terminate the study for futility if the lower bound of the 95% CI for the treatment difference (MK-8521 minus liraglutide) in change from baseline is above 0.
- Body weight futility criterion: Potentially terminate the study for futility if the posterior probability is < 5% that the true placebo-adjusted weight loss with MK-8521 is at least 4.5 kg.

The futility criteria will be non-binding. If either criterion is met, the unblinded interim data will be reviewed with additional individuals with programmatic oversight and the decision to terminate or continue the study will be made based on assessment of the overall data and in consideration of programmatic goals.

Details including safety endpoints (AEs and change from baseline in heart rate) and review criteria will be provided in the siDMC charter.

Power and sample size will be re-assessed based only on the conditional standard deviation at the interim analysis and will be performed by the unblinded statistician. If any sites are identified as having low compliance as defined in Section 8.2.4, the goal of the sample size adjustment will be to ensure adequate power in the mFAS population. The conditional standard deviation for A1C and body weight will be estimated from the cLDA model in the mFAS population. Implementation details will be provided in the siDMC charter.

As stated in Section 8.2.7, the initial sample size (40 per arm) will provide 85% power for the A1C hypothesis and 87% power for the body weight hypothesis, resulting in 74% overall power for success in testing both hypotheses. The sample size will be increased, if necessary, so that there is at least 80% power for each individual hypothesis for A1C and body weight, and at least 74% overall power for both hypotheses in the mFAS population. A conservative estimate of SD will be used to calculate the power and sample size. The following rules will be used for adjusting the sample size:

- For A1C, 0.1% will be added to the point estimate of conditional SD from the interim data. For example, if the point estimate is 1.1%, 1.2% will be used in the sample size computation;
- For body weight, 0.2 kg will be added to the point estimate of conditional SD from the interim data. For example, if the point estimate is 2.7 kg, 2.9 kg will be used in the sample size computation.

If necessary, the sample size will be increased to the minimum sample size that meets the power criteria above, subject to a maximum of 45 subjects per arm in the mFAS population and a total maximum of 200 subjects randomized. If the power criteria above cannot be met within these sample size constraints, the trial will continue using the maximum permissible sample size under these constraints.

Table 14 Summary of Planned Efficacy and Safety Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
• Change in A1C at Week 12 • Change in body weight at Week 12 • Change in HR at Week 12 • Key safety endpoints (including serious adverse events, adverse events leading to discontinuation)	When at least 50% of randomized subjects either complete Week 12 or discontinue prior to Week 12	• Program planning • Sample size re-estimation, • Study termination for futility.

8.2.10 Compliance (Medication Adherence)

The computation of compliance in the ASaT population will be based on the study medication case report form.

For each subject, percent compliance will be calculated using the following formula:

$$\text{Compliance} = \frac{\text{Number of Compliant Days}}{\text{Number of Days in the Treatment Period}} \times 100\%.$$

A day within the Treatment period will be considered a compliant day if the subject reports taking the prescribed number of injections from the correct vials.

The "Number of Days in Treatment Period" is defined for each subject as the total number of days from the first dose of study medication to the last day of study medication.

Summary statistics will be provided on percent compliance by treatment group.

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 15

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 15 Product Descriptions

Product Name & Potency	Dosage Form
MK-8521: 0.6mg/mL and matching Placebo	Sterile Solution for Injection

All other supplies not indicated in Table 15 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

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

Subjects will receive blinded weekly kits containing 20 vials of MK-8521 or MK-8521 Placebo for the run in and treatment phases of the study. Syringes will NOT be provided in the kit boxes.

9.3 Clinical Supplies Disclosure

The liraglutide arm of this 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.

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity for MK-8521 or MK-8521 placebo groups of this trial. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will provide random code/disclosure envelopes or lists to the emergency unblinding call center.

Treatment 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 and reason) 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. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

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 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.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

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 member 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 or through a secure password-protected electronic portal 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/ERC 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 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 discarding 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 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.clinicaltrialregister.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 trials 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.

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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 plasma, serum and leftover DNAplasma, serum and leftover DNAplasma, serum and leftover DNAplasma, serum and leftover DNA specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The plasma, serum and leftover DNAplasma, serum and leftover DNA specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

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 Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

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, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first 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 first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. 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 the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. 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 Merck using the designated mailbox (PPD and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for 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 specimen destruction can not 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain

instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

13. Questions

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

14. References

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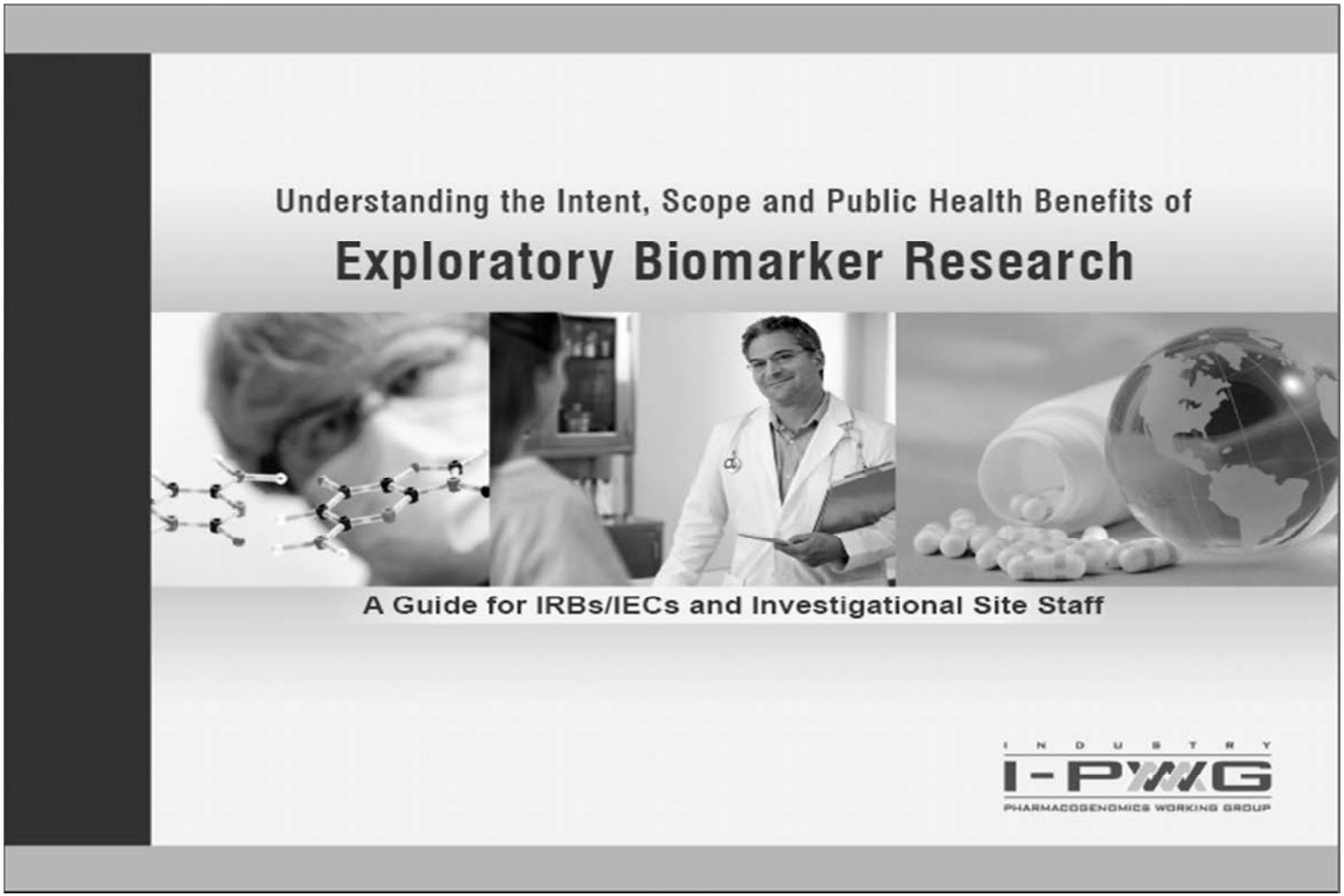
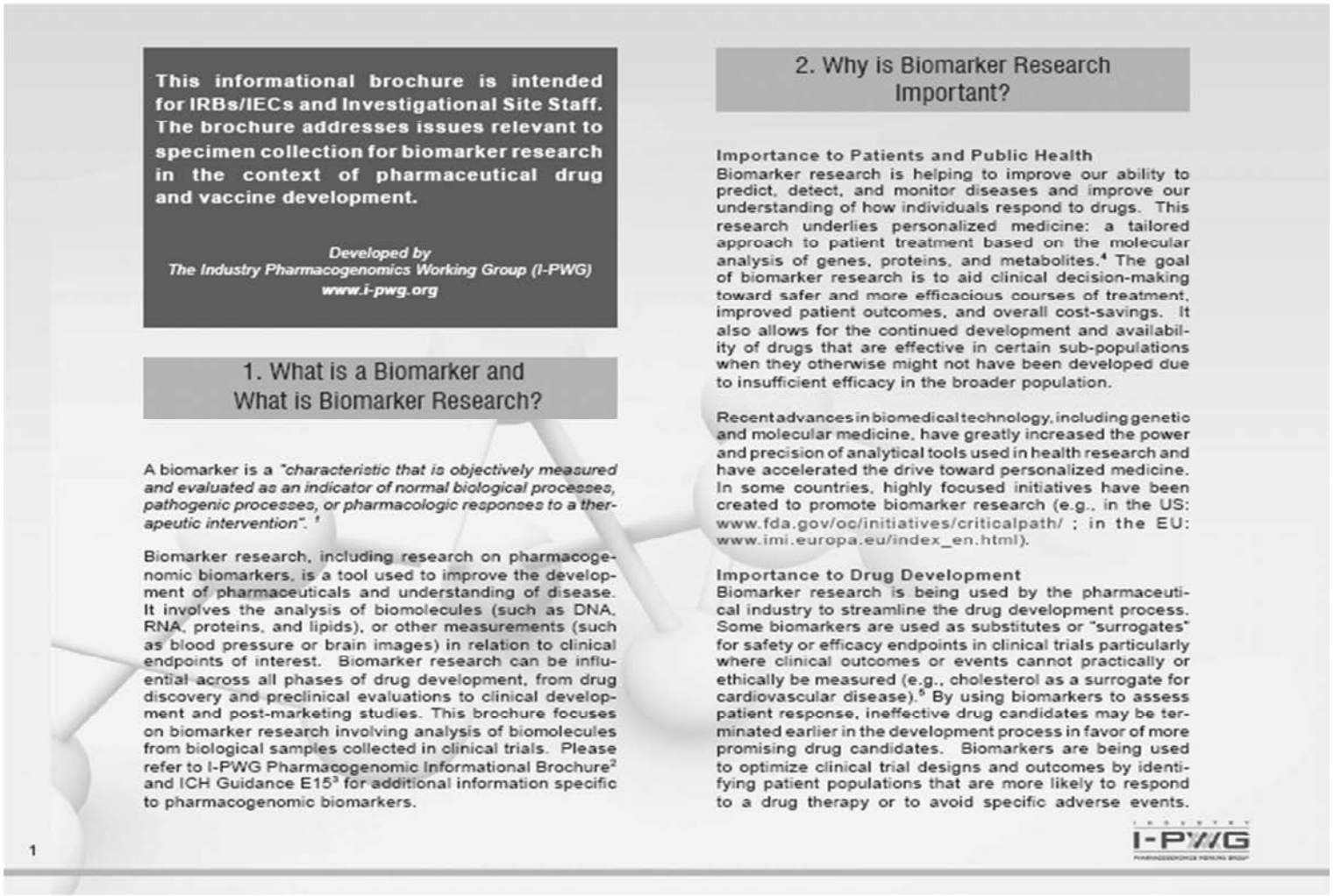
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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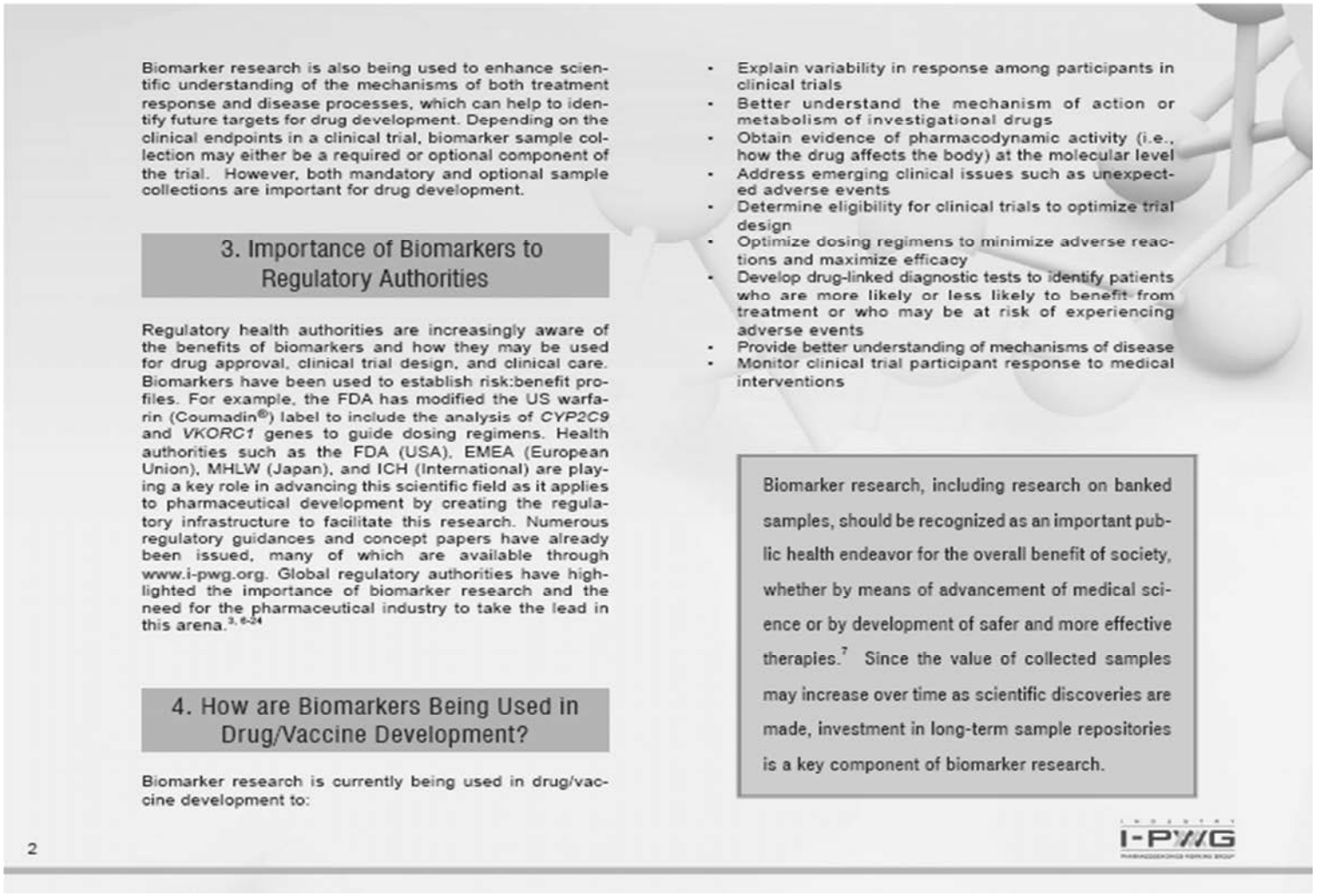
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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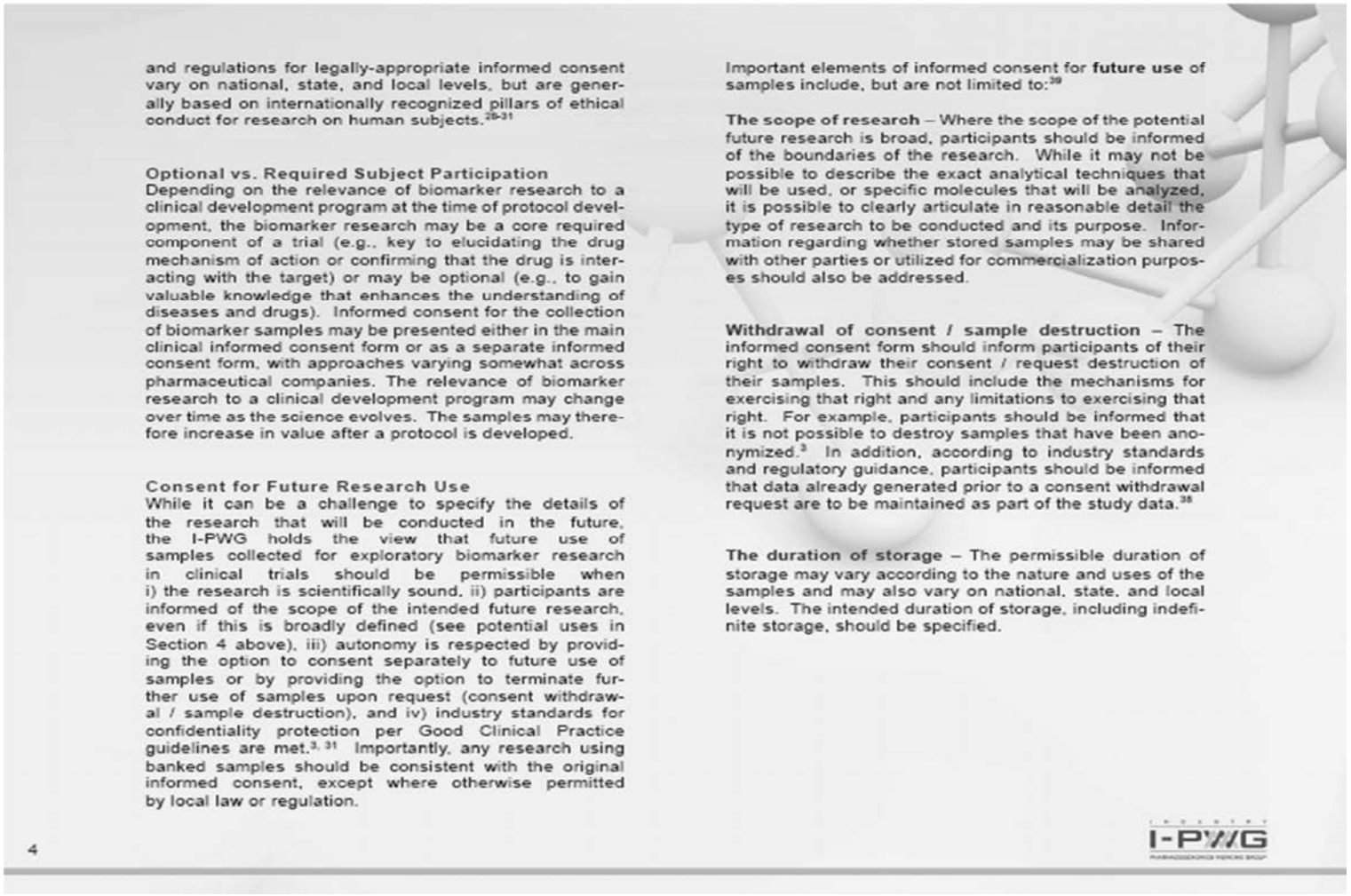


and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

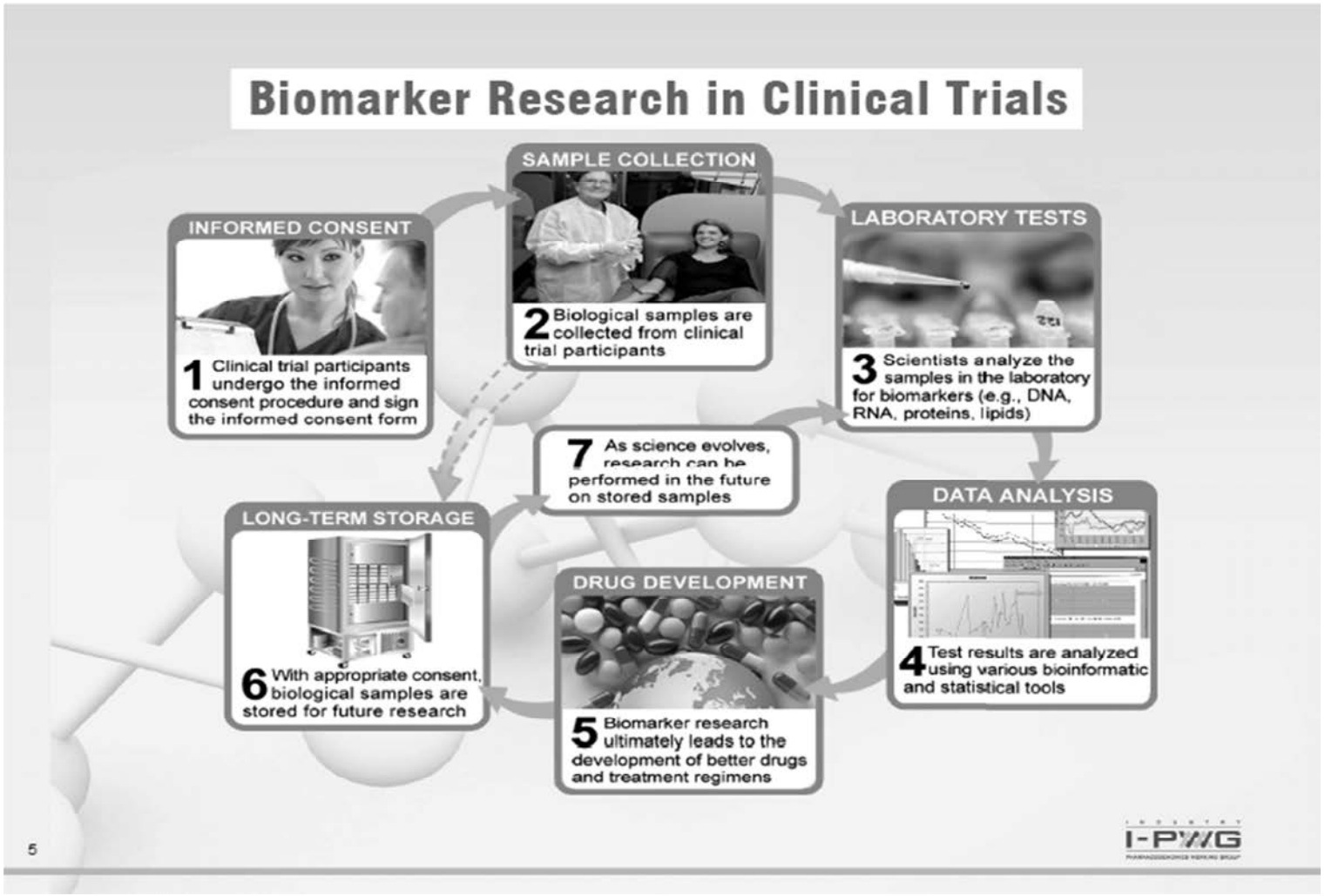
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.


Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits
While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks
Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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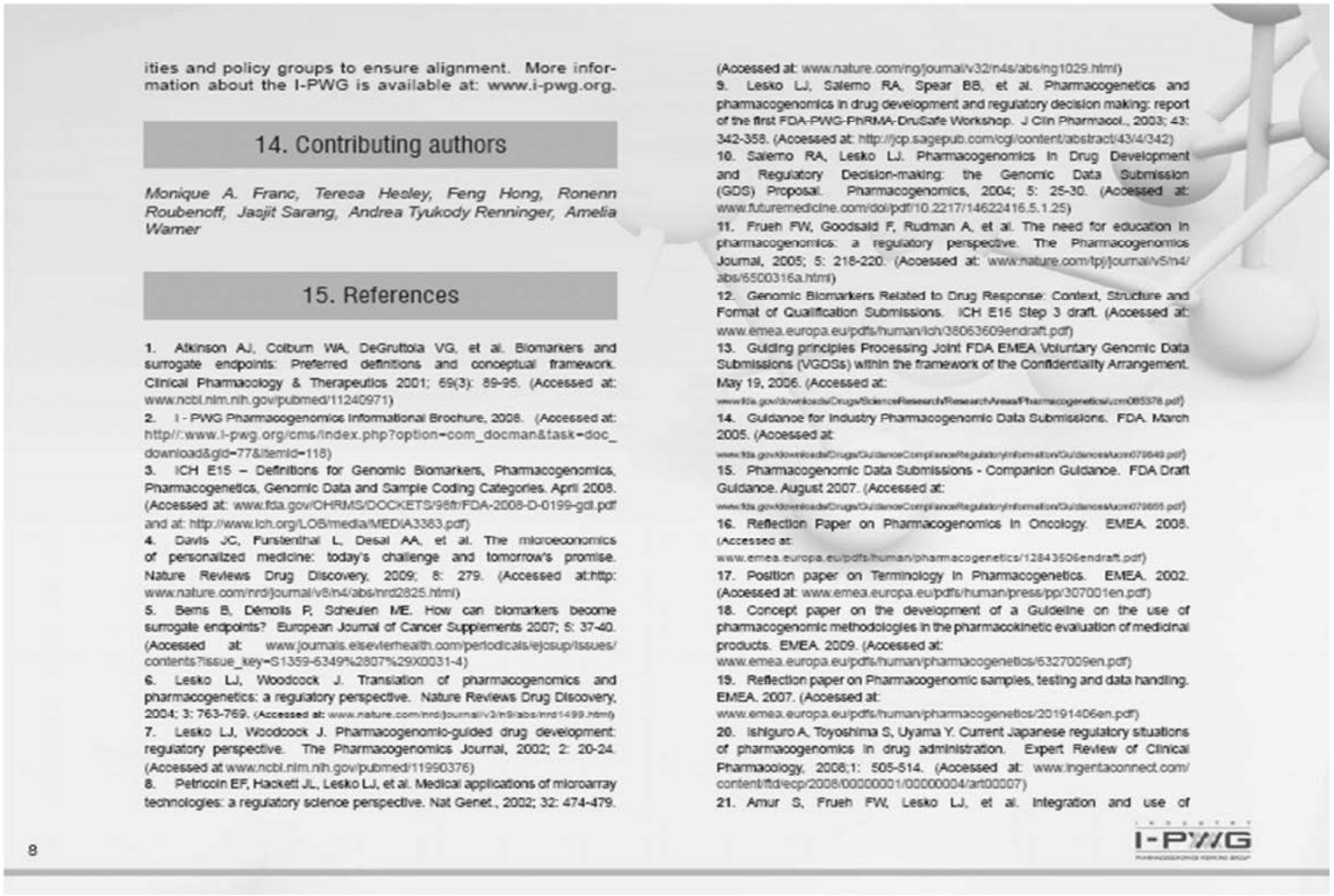

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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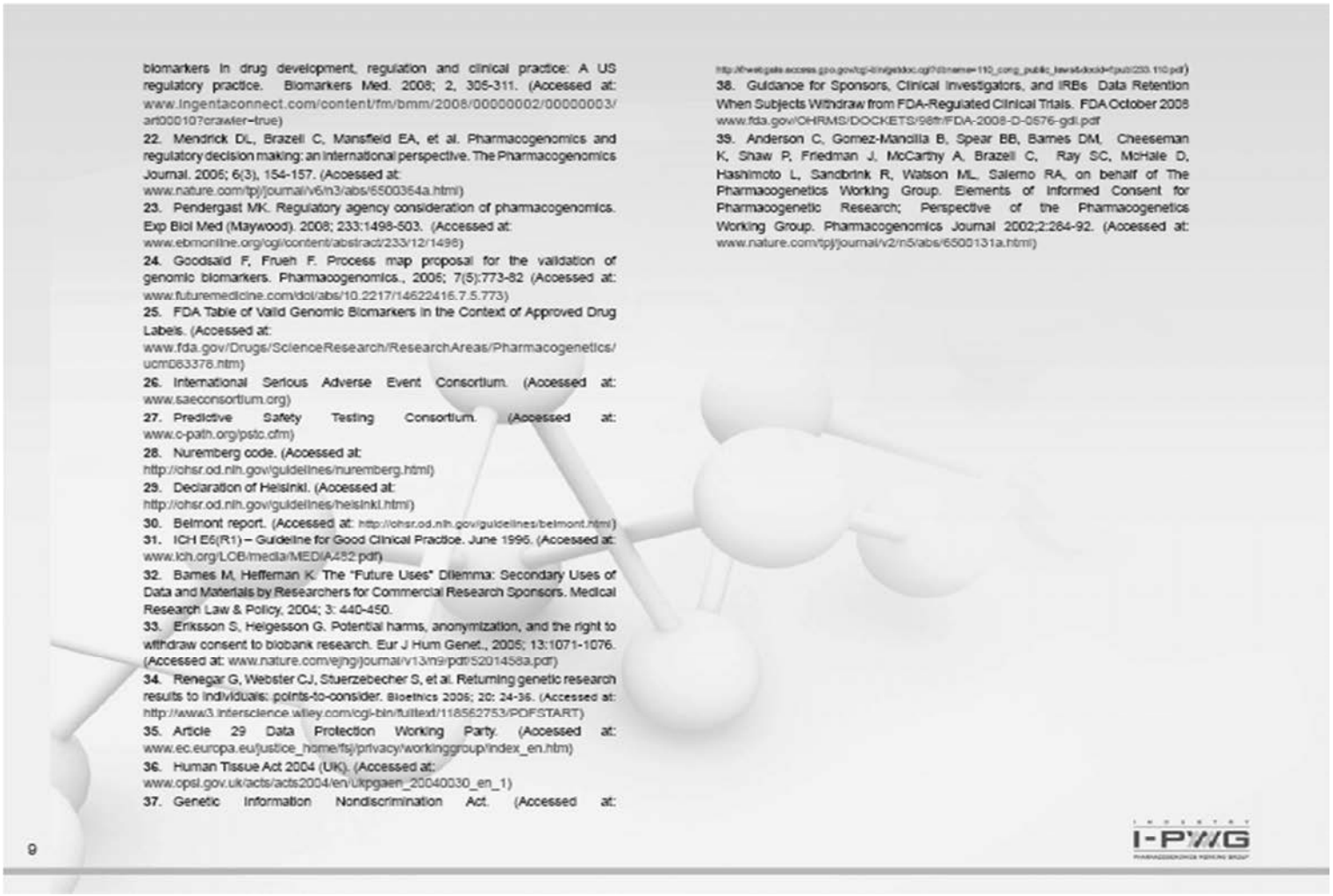

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12.4 Mapping of Relative Day Ranges to Weeks

The following will be used to map the relative day ranges to weeks, as described in **Section 8.2**.

Mapping of Relative Day Ranges to Weeks

Required Phase	Relative Day Range	Week
	Day Relative to Start of Trial	
—	Visit <2 and Day <1	min(Day/7[†], -2)
Placebo Run-in	Visit ≥2 and Visit <3 and Day <1	-2
Placebo Run-in	Visit ≥3 and Day ≤1	0
Treatment	2 ≤ Day ≤ 52	6
Treatment	53 ≤ Day ≤ 73	9
Treatment	74 ≤ Day	12

[†] Truncated to the largest integer less than or equal to this ratio.

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 – 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	